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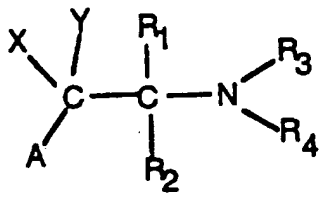

(I)

(57) Abstract

The present invention relates to novel alkylamino derivatives of formula (I). These compounds exhibit a high selectivity and a high affinity for sigma 2 receptor and therefore are useful in the treatment of central nervous system disorders as well as other disorders modulated by this receptor.

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DESCRIPTION

NOVEL ALKYLAMINO DERIVATIVES AS SIGMA 2 SELECTIVE LIGANDS

Technical Field

The present invention relates to novel alkylamino derivatives, pharmaceutical compositions comprising such compounds and the use of such compounds in the treatment of central nervous system disorders as well as several other disorders. The pharmaceutically active compounds of this invention are highly selective and high affinity sigma 2 ligands.

Background Art

The recently identified brain sigma receptors/binding sites are potential targets for development of antipsychotic drugs that lack the adverse effects associated with currently available dopaminergic D2 antipsychotic agents [J.M. Walker , W.D. Bowen, F.O. Walker, R.R. Matsumoto, B. de Costa and K.C. Rice, Pharmacological Reviews, 1990, 42, 355-402; G. Debonnel, J. Psychiatr. Neurosci., 1993, 18, 4, 157-172]. The term "receptor" as used herein refers to membrane-bound receptors and to other binding sites. The existence of at least two sigma receptor subtypes, sigma 1 and sigma 2, has been confirmed and a classification of sigma binding sites has been proposed [R. Quirion, W.D. Bowen, Y. Itzhak, J.L. Junien, J.M. Musacchio, R.B. Rothman, T.P. Su, W. Tam and D.P. Taylor, TiPS, 1992, 13, 85-86].

Sigma 1 binding sites are characterized by high affinity for haloperidol, Di-o-Tolyl Guanidine (DTG) and (+) benzomorphans such as (+) pentazocine. Sigma 2 binding sites are characterized by high affinity for haloperidol and DTG but low affinity for the (+) benzomorphans. Sigma 1 ligands have shown gastro-intestinal effects ; moreover, sigma 1 sites appear to mediate the inhibition by sigma ligands of the muscarinic acetylcholine receptor

phosphoinositide response. Sigma 1 binding sites are not only present in the brain but also on splenocytes. Such sigma ligands may inadvertently suppress the immune system [H.H. Garza, S. Mayo, W.D. Bowen, B.R. DeCosta and D.J.J. Carr, J. of Immunology, 1993, 151, 9, 4672-4680]. Sigma 2 binding sites are abundant in liver [A.E. Bruce, S.B. Hellewell and W.D. Bowen, Soc. Neurosci. Abstr., 1990, 16, 370; A.S. Basile, I.A. Paul and B. DeCosta, Eur. J. Pharmacol. Mol. Pharm. Sect., 1992, 227, 95-98], kidney [W.D. Bowen, G. Feinstein and J.S. Orringer, Soc. Neurosci. Abstr., 1992, 18, 456, abstract 195.8] and heart [M. Dumont and S. Lemaire, Eur. J. Pharmacol., 1991, 209, 245-248].

In the brain, sigma 2 binding sites are present in hypothalamus, cerebellum and pons medulla. In rat brain, they are more abundant than sigma 1 sites in hippocampus, frontal and posterior cortex [D. J. Mc Cann, A. D. Weissmann and T.P. Su, Soc. Neurosci abstr. 1992, 18, 22, abstract 16.5]. Guinea pig hippocampus membranes possess also sigma 2 binding sites which are selectively labelled by [^{3}H] BIMU [D.W. Bonhaus, D.N. Loury, L.B. Jakeman, Z. To, A. DeSouza, R.M. Eglen and E.H.F. Wong, J. Pharmacol. Exp. Ther., 1993, 267, 2, 961-970]. The association of sigma 2 binding sites with cortical and limbic areas provide support to the interest of such compounds in the treatment of psychiatric disorders [D.C. Mash and C.P. Zabetian, Synapse, 1992, 12, 195-205]. Sigma 2 binding sites have been suspected to mediate motor effects especially dystonia [R.R. Matsumoto, M.K. Hemstreet, N.L. Lai, A. Thurkauf, B.R. DeCosta, K.C. Rice, S.B. Hellewell, W.D. Bowen and J.M. Walker, Pharmacol. Biochem. Behav., 1990, 36, 151-155]; however, there is no evidence for such effect in primate models of extrapyramidal dysfunction [L.T. Meltzer, C.L. Christoffersen, K.A. Serpa, T.A. Pugsley, A. Razmpour and T.G. Heffner, Neuropharmacology, 1992, 31, 9, 961-967].The clinically effective dopaminergic antipsychotic haloperidol shows a high affinity to the two sigma subtypes; however, the CNS active reduced metabolite of haloperidol shows a better affinity and selectivity for sigma 2 receptors towards dopaminergic D2 receptors than haloperidol [J.C. Jaen, B.W. Caprathe, T.A. Pugsley, L.D. Wise and H. Akunne, J. Med. Chem., 1993, 36, 3929-3936]. In fact, the understanding of the pharmacology, distribution and function of sigma 2 binding sites has been hampered by the lack of selective agents.

Few agents bind with a high affinity to sigma 2 binding sites [M. Abou-Gharbia, S.Y. Ablordeppey and R.A. Glennon, Annual Reports in Medicinal Chemistry, 1993, 28, 1-10]. Ifenprodil has a marked selectivity for sigma 2 sites but it binds also to polyamine and alpha-1 receptors [K. Hashimoto, C.R. Mantione, M.R. Spada, J.L. Neumayer and E.D. London, Eur. J. Pharmacol. Mol. Pharm. Sect., 1994, 266, 66-77]. [^{3}H] BIMU has been proposed as a selective sigma 2 ligand with Ki = 32 nM [D.W. Bonhaus, D.N. Loury, L.B. Jakeman, Z. To, A. DeSouza, R.M. Eglen and E.H.F. Wong, J. Pharmacol. Exp. Ther., 1993, 267, 2, 961-970]; however, despite a good selectivity towards sigma 2, this compound is also a highly potent 5-HT3 and 5-HT4 serotonin ligand. WO 93/00313 relates to sigma receptor ligands and their sigma 1/ sigma 2 selectivity; three compounds present an interesting sigma 2 selectivity, they belong to the phenyl piperazine class and are also high affinity 5-HT1A serotonin ligands [R.A. Glennon, N.A. Naiman, R.A. Lyon and M. Titeler, J. Med. Chem., 1988, 31, 1968-1971]. Sub-nanomolar affinity sigma binding sites ligands have been presented as sigma 2 ligands [J. Perregaard, E.K. Moltzen, E. Meier, C. Sanchez and J. Hyttel, Soc. Neurosci. Abstr., 1993, 19, 1868, abstract 763.16], but no data on their sigma selectivity has been shown and they also bind to alpha 1 receptor with a moderate to high affinity. The 5, 6, 7, 8, 9, 10-hexahydro-7,10-iminocyclohept[b]indoles have been identified as selective sigma 2 ligands [R.E. Mewshaw, R.G. Sherrill, R.M. Mathew, C. Kaiser, M.A. Bailey and E.W. Karbon, J. Med. Chem., 1993, 36, 343-352] with moderate to high affinity. A new approach to sigma 2 ligands has been recently disclosed: the polyamino sigma ligands described were moderatly potent and selective for sigma 2 site [B.R. DeCosta, X.S. He, C. Dominguez, J. Cutts, W. Williams and W.D. Bowen, J. Med. Chem., 1994, 37, 314-321].

Extensive literature exists relating to heteroaryl alkylamino derivatives; however there is very little data concerning heteroaryl groups like the naphtosultam ring. EP 546388 discloses heteroaryl methyl piperidino derivatives of chromanes, without examples of naphtosultam compounds. Alkylamino naphtosultam derivatives are described with examples in EP 352613, these compounds are claimed as 5-HT1A ligands. EP 350403, EP

429341 and WO 91/16323 disclose series of naphtosultam derivatives as 5-HT2 antagonists and 5-HT reuptake inhibitors.

The present invention relates to a substituted (preferentially adamantyl, cycloalkyl)hydroxy-amino and diamino derivatives. Numerous phenyl ethanolamino derivatives exhibit important pharmaceuticals properties [Pharmaceutical Chemistry Vol. 1 : drug synthesis, H.J. Roth, A. Kleemann and T. Beisswenger, Ellis Horwood limited, Chichester England, 37-69]. For example, benzyl-piperidino derivatives like Ifenprodil and its derivatives belong to this class and are known to interact with sigma, adrenergic and glutamatergic receptors [B.L. Chenard, I.A. Shalaby, B.K. Koe, R.T. Ronau, T.W. Butler, M.A. Prochniak, A.W. Schmidt and C.B. Fox, J. Med. Chem., 1991, 34, 3085-3090]. Surprisingly, the cycloalkyl and adamantyl ethanolamino derivatives of the present invention show a completely different and selective binding profile.

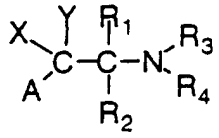
EP 518 216 disdoses certain N-[arylethyl]-N-alkyl-2-(1-pyrrolidinyl)ethylamine compounds for CNS disorders. WO 93/22279 discloses 3-phenyl-1,2-propanediamine derivatives having selective affinity for sigma receptors. These compounds are potent preferentially sigma 1 ligands; no heteroaromatic derivatives are described and they are not substituted in a position by a cycloalkyl group. WO 93/10073 relates to ethylenediamine derivatives as substance P receptor antagonists; the general formula refers to secondary amino compounds. US 5,039,706 describes benzylamine derivatives having phospholipase A2 inhibiting properties, some examples of phenyl-propane diamino compounds are given.

The compounds described above do not show the sigma 2 receptor selectivity and affinity demonstrated by the compounds of the present invention.

The present invention resides in the discovery of a group of selective and high affinity sigma 2 binding site ligands. The inhibition constant Ki for sigma 2 binding site is of at least 50 nM and these new ligands have at least a 5 fold greater affinity for sigma 2 than sigma 1 binding sites and dopaminergic (D1, D2), serotoninergic (5-HT1A, 5-HT2, 5-HT3), adrenergic (alpha and beta) and phencyclidine (PCP) receptors. Such binding profile makes the compounds of the present invention advantageous over compounds of the prior art.

Disclosure of Invention

Novel alkylamino derivatives of the invention which conform to the formula :



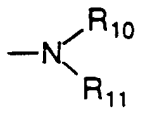
(1)

When X represents cycloalkylalkyl or adamantyl, Y represents hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, adamantyl, aryl, arylalkyl, heteroaryl or heteroarylalkyl; wherein each of said aryl and heteroaryl groups may optionally be substituted with one or more substituents, each of the said substituents being independently selected from halo, nitro, cydoalkyl, alkenyl, alkyl optionally substituted with one to three fluorine atoms, hydroxy, alkoxy optionally substituted with one to three fluorine atoms, phenyl, amino, alkylamino, carbamoyl, sulfamoyl, carboxyalkyl, cyano or alkynyl.

When X represents cycloalkyl, Y represents hydrogen, alkyl, alkenyl or cycloalkyl.

A represents the group -O-R_9 in which R_9 represents hydrogen, alkyl, cycloalkyl, cycloalkylalkyl, alkenyl, aryl, arylalkyl, hydroxyalkyl, carboxyalkyl or carboxyaryl;

or A represents the group



R_{10} and R_{11} represent independently hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, hydroxyalkyl, carboxyalkyl, halcalkyl, halcalkoxyalkyl, aryl, arylalkyl,

heteroaryl or heteroarylalkyl; each of the said aryl and heteroaryl groups may optionally be substituted with one or more substituents, each of the said substituents being independently selected from halo, nitro, cycloalkyl, alkenyl, alkyl optionally substituted with from one to three fluorine atoms, hydroxy, alkoxy optionally substituted with one to three fluorine atoms, phenyl, amino, alkylamino, carboxy, carbamoyl, sulfamoyl, carboxyalkyl, cyano or alkynyl.

R_{10} and R_{11} taken together may form a ring corresponding to the formula :

$$-(CH_2)_m-D-(CH_2)_m-$$

where D represents a single bond, oxygen, sulfur or a nitrogen atom substituted by hydrogen, alkyl, cycloalkyl, alkenyl, cycloalkylalkyl, aryl or arylalkyl;

m is a number selected from 1 to 3;

R_{10} and R_{11} taken together with the nitrogen atom may form a 3-10 atom unsaturated heterocyclic ring which optionally contains 1 to 4 further heteroatom selected from oxygen, nitrogen and sulfur; such heterocyclic group may optionally be substituted with one or more substituents, each of the said substituents being independently selected from halo, nitro, cycloalkyl, alkenyl, alkyl optionally substituted with one to three fluorine atoms, hydroxy, alkoxy optionally substituted with one to three fluorine atoms, phenyl, amino, alkylamino, carbamoyl, sulfamoyl, carboxy,carboxyalkyl, cyano or alkynyl.

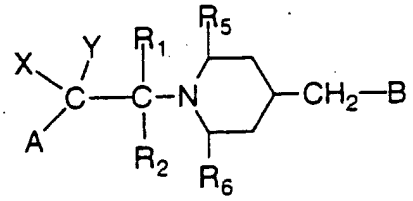
or Y and A taken together may form oxo or hydroxyimino.

R_1 and R_2 which may be the same or different, are hydrogen, alkyl, cycloalkyl, hydroxyalkyl or alkenyl.

R_3 represents alkyl, cycloalkyl, hydroxyalkyl or alkenyl;

R_4 represents the group $-(CH_2)_p-B$ where p is a number selected from 3 to 8;

or R_3 and R_4 together with the intervening nitrogen atom represent a piperidine ring which is substituted as depicted in formula **(II)** :

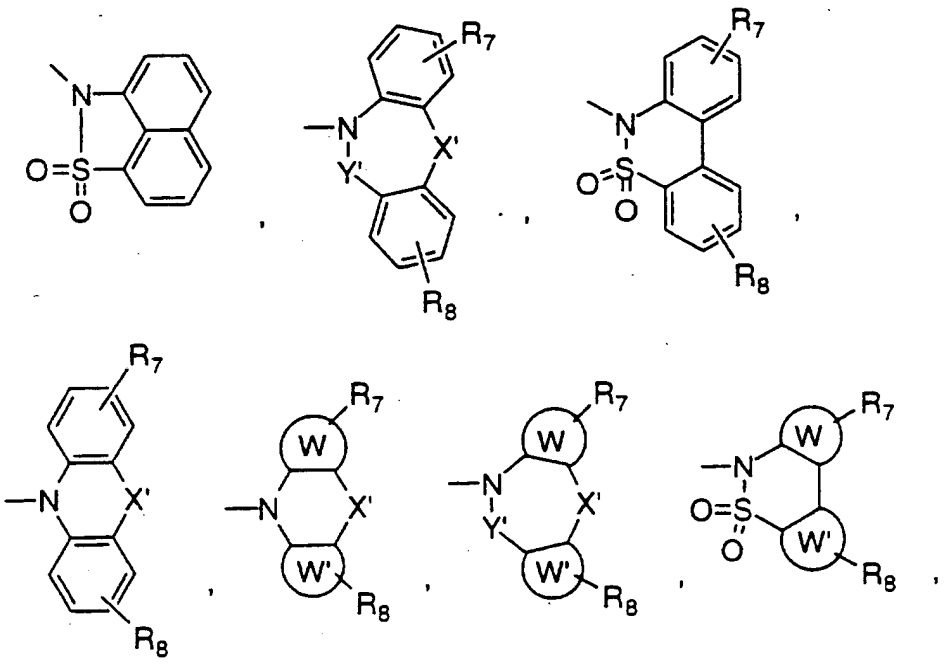


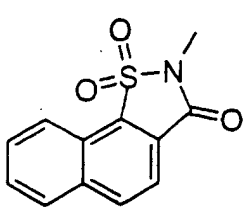
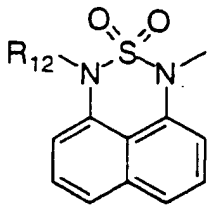
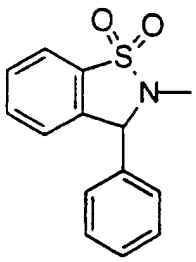
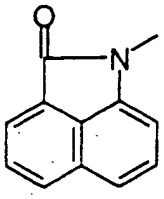
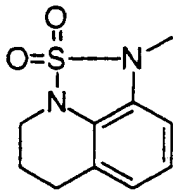
(II)

where R_5 and R_6 represent independently hydrogen or alkyl;

or R_5 and R_6 together with the intervening atom represent a 5 to 7 heterocyclic ring.

B is a heteroaryl group of formula

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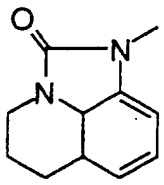


R_7 and R_8 are independently selected from hydrogen, halo, nitro, cycloalkyl, alkenyl, alkyl optionally substituted with one to three fluorine atoms, hydroxy, alkoxy optionally substituted with one to three fluorine atoms, phenyl, amino, alkylamino, carbamoyl, sulfamoyl, carboxyalkyl, cyano or alkynyl.

R_{12} is selected from hydrogen or alkyl.

X' represents a single bond, $-CH_2-$, $-CH=CH-$, $-CH_2-CH_2-$, S, $-S-CH_2-$, $-S(O)-$, $-S(O)_2-$, $-S(O)-CH_2-$, $-S(O)_2-CH_2-$, O, $-O-CH_2-$, $N(R_{13})$, $-N(R_{13})-CH_2-$, $-N(R_{13})-S(O)_2-$, C(=O), $-C(=O)-CH_2-$, $-C(=O)-O-$ or $-C(=O)-N(R_{13})-$;

Y' represents $-CH_2-$ or C(=O) ;

W and W' represent independently a benzene ring or heteroaryl group of 5 to 7 atoms which contains one oxygen atom , one sulfer atom or one or two nitrogen atoms, provided that at least one of W and W' is heteroaryl group.

R_{13} represents hydrogen or alkyl.

In the above definition, "alkyl" includes C_1-C_6 alkyl group such as methyl group, ethyl group, propyl group, isopropyl group, butyl group, isobutyl group, sec-butyl group, tert-butyl group, pentyl group, isopentyl group, neopentyl group, tert-pentyl group, hexyl group or the like.

"Cycloalkyl" includes C_3-C_6 cycloalkyl group such as cyclopropyl group, cyclobutyl group, cyclopentyl group, cyclohexyl group or the like.

"Cycloalkyalkyl" includes C_3-C_6 cycloalkyl-C_1-C_3 alkyl group such as cyclopropylmethyl group, cyclopropylethyl group, cyclopropylpropyl group, cyclobutylmethyl group, cyclobutylethyl group, cyclopentylmethyl group, cyclohexylmethyl group or the like.

"Alkenyl" includes C_3-C_6 alkenyl group such as 1-propenyl group, allyl group, isopropenyl group, 1-butenyl group, 3-butenyl group, 1-pentenyl group, 2-pentenyl group, 3-pentenyl group, 4-pentenyl group, 1-hexenyl group, 2-hexenyl group or the like.

"Alkynyl" includes C_3-C_6 alkynyl group such as 2-propynyl group, 3-butynyl group, 4-pentynyl group, 5-hexynyl group or the like.

"Alkoxy" includes C_1-C_6 alkoxy group such as methoxy group, ethoxy group, propoxy group, isopropoxy group, butoxy group, isobutoxy group, tert-butoxy group, pentyloxy group, hexyloxy group or the like.

"Halo" includes atoms such as fluorine atom, chlorine atom, bromine atom, iodine atom or the like.

"Alkylamino" includes C_1-C_6 alkylamino group such as methylamino group, ethylamino group, propylamino group, butylamino group, pentylamino group, hexylamino group, dimethylamino group, methylethylamino group, diethylamino group, dipropylamino group or the like.

"Carboxyalkyl" includes carboxy-C_1-C_6 alkyl group such as carboxymethyl group, 2-carboxyethyl group, 3-carboxypropyl group, 4-carboxybutyl group, 5-carboxypentyl group, 6-carboxyhexyl group or the like.

"Hydroxyalkyl" includes hydroxy-C2-C6 alkyl group such as 2-hydroxyethyl group, 3-hydroxypropyl group, 4-hydroxybutyl group, 5-hydroxypentyl group, 6-hydroxyhexyl group or the like.

"Haloalkyl" includes halogenated-C_1-C_3 alkyl group such as chloromethyl group, dichloromethyl group, trichloromethyl group, fluoromethyl group, difluoromethyl group, trifluoromethyl group, bromomethyl group, 1-chloroethyl group, 1,1-dichloroethyl group, 2-chloroethyl group, 2,2-

dichloroethyl group, 2,2,2-trichloroethyl group, 1-fluoroethyl group, 1,1-difluoroethyl group, 2-fluoroethyl group, 2,2-difluoroethyl group, 2,2,2-trifluoroethyl group, 2-bromoethyl group, 3-chloropropyl group, 3-fluoropropyl group, 3-bromopropyl group or the like.

"Haloalkoxyalkyl" includes halogenated-C_1-C_3 alkoxy-C_1-C_3 alkyl group such as chloromethoxymethyl group, chloromethoxyethyl group, chloromethoxypropyl group, fluoromethoxymethyl group, fluoromethoxyethyl group, trifluoromethoxymethyl group, trifluoromethoxyethyl group, trifluoromethoxypropyl group, bromomethoxymethyl group, bromomethoxyethyl group, bromomethoxypropyl group, 1-chloroethoxymethyl group, 2-chloroethoxymethyl group, 2-chloroethoxyethyl group, 2-chloroethoxypropyl group, 2-fluoroethoxymethyl group, 2-fluoroethoxyethyl group, 2-fluoroethoxypropyl group, 2,2,2-trifluoroethoxymethyl group, 3-chloropropoxymethyl group, 3-fluoropropoxymethyl group or the like.

"Aryl" includes C_6-C_{10} aryl group such as phenyl group, 1-naphtyl group, 2-naphtyl group or the like.

"Arylalkyl" includes C_6-C_{10} aryl-C_1-C_3 alkyl group such as benzyl group, 1-phenylethyl group, 2-phenylethyl group, 1-phenylpropyl group, 2-phenylpropyl group, 3-phenylpropyl group, 1-naphtylmethyl group, 2-naphtylmethyl group or the like.

"Carboxyaryl" includes carboxy-C_6-C_{10} aryl group such as 2-carboxyphenyl group, 3-carboxyphenyl group, 4-carboxyphenyl group, 2,6-dicarboxyphenyl group, 2,4,6-tricarboxyphenyl group, 2-carboxy-1-naphthyl group, 3-carboxy-1-naphthyl group, 4-carboxy-1-naphthyl group, 1-carboxy-2-naphthyl group, 3-carboxy-2-naphthyl group, 4-carboxy-2-naphthyl group, 1,5-dicarboxy-2-naphthyl group or the like.

"Heteroaryl" includes 5-10 membered heterocyclic group containing 1 to 4 hetero atoms selected from oxygen atom, sulfur atom and nitrogen atom to form a ring such as furyl group (furan ring), benzofuranyl group (benzofuran ring), isobenzofuranyl group (isobenzofuran ring), thienyl group (thiophene ring), benzothiophenyl group (benzothiophene ring), pyrrolyl group (pyrrole ring), imidazolyl group (imidazole ring), pyrazolyl group (pyrazole ring), thiazolyl group (thiazole ring), isothiazolyl group (isothiazole ring), triazolyl group (triazole ring), tetrazolyl group (tetrazole ring), pyridyl group (pyridine ring), pyrazynyl group (pyrazine ring), pyrimidinyl group (pyrimidine ring), pyridazinyl group (pyridazine ring), indolyl group (indole ring), isoindolyl group (isoindole ring), benzoimidazolyl group (benzoimidazole ring), purinyl group (purine ring),

quinolyl group (quinoline ring), phtalazinyl group (phtalazine ring), naphtyridinyl group (naphtyridine ring), quinoxalinyl group (quinoxaline ring), cinnolinyl group (cinnoline ring), pteridinyl group (pteridine ring), oxazolyl group (oxazole ring), isooxazolyl group (isooxazole ring), benzooxazolyl group (benzooxazole ring), furazanyl group (furazan ring) or the like.

"Heteroarylalkyl" includes heteroaryl-C_1-C_3 alkyl group, wherein examples of heteroaryl are the same as those illustrated in the above definition, such as 2-furylmethyl group, 3-furylmethyl group, 2-thienylmethyl group, 3-thienylmethyl group, 1-imidazolylmethyl group, 2-imidazolylmethyl group, 2-thiazolylmethyl group, 1-pyridylmethyl group, 2-pyridylmethyl group, 3-pyridylmethyl group, 4-pyridylmethyl group, 1-quinolylmethyl group, 2-quinolylmethyl group or the like.

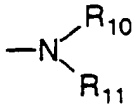
Preferred compounds of the present invention are compounds of formula (I) wherein :

When X represents C_3-C_6 cycloalkyl-C_1-C_3-alkyl or adamantyl, Y represents hydrogen, C_1-C_6 alkyl, C_3-C_6 alkenyl, C_3-C_6 alkynyl, C_3-C_6 cycloalkyl, C_3-C_6 cycloalkyl-C_1-C_3-alkyl, adamantyl, aryl selected from phenyl and naphthyl, aryl-C_1-C_3-alkyl; wherein each of said aryl group may optionally be substituted with one to three substituents, each of the said substituents being independently selected from halo, nitro, C_3-C_6 cycloalkyl, C_3-C_6 alkenyl, C_1-C_6 alkyl optionally substituted with one to three fluorine atoms, hydroxy, C_1-C_6 alkoxy optionally substituted with one to three fluorine atoms, phenyl, amino, C_1-C_6 alkylamino, carbamoyl, sulfamoyl, carboxy-C_1-C_6-alkyl, cyano or C_3-C_6 alkynyl.

When X represents C_3-C_6 cycloalkyl, Y represents hydrogen, C_1-C_6 alkyl, C_3-C_6 alkenyl or C_3-C_6 cycloalkyl.

A represents the group -O-R_9 in which R_9 represents hydrogen, C_1-C_6 alkyl, C_3-C_6 cycloalkyl, C_3-C_6 cydoalkyl-C_1-C_3-alkyl, C_3-C_6 alkenyl, phenyl, phenyl-C_1-C_3-alkyl, hydroxy-C_2-C_6-alkyl, carboxy-C_1-C_3-alkyl or carboxyphenyl;

or A represents the group



R_{10} and R_{11} represent independently hydrogen, C_1-C_6 alkyl, C_3-C_6 alkenyl, C_3-C_6 alkynyl, C_3-C_6 cycloalkyl, phenyl or phenyl-C_1-C_3-alkyl; phenyl group may optionally be substituted with one to three substituents, each of the said substituents being independently selected from halo, nitro, C_1-C_6 alkyl, hydroxy, amino, carboxy or cyano;

R_{10} and R_{11} taken together may form a ring corresponding to the formula :

$$-(CH_2)_m\text{-}D\text{-}(CH_2)_m-$$

where D represents a single bond, oxygen, sulfur or a nitrogen atom substituted by hydrogen or C_1-C_6 alkyl;

m is a number selected from 1 to 3;

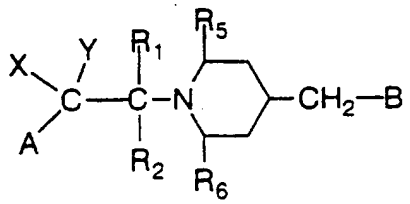
or Y and A taken together may form oxo or hydroxyimino.

R_1 and R_2 which may be the same or different, are hydrogen, C_1-C_3 alkyl, C_3-C_6 cycloalkyl, hydroxy-C_2-C_3 alkyl or C_3-C_6 alkenyl.

R_3 represents C_1-C_3 alkyl, C_3-C_6 cycloalkyl, hydroxy-C_2-C_3-alkyl or C_3-C_6-alkenyl;

R_4 represents the group $-(CH_2)_p$-B where p is a number selected from 3 to 6;

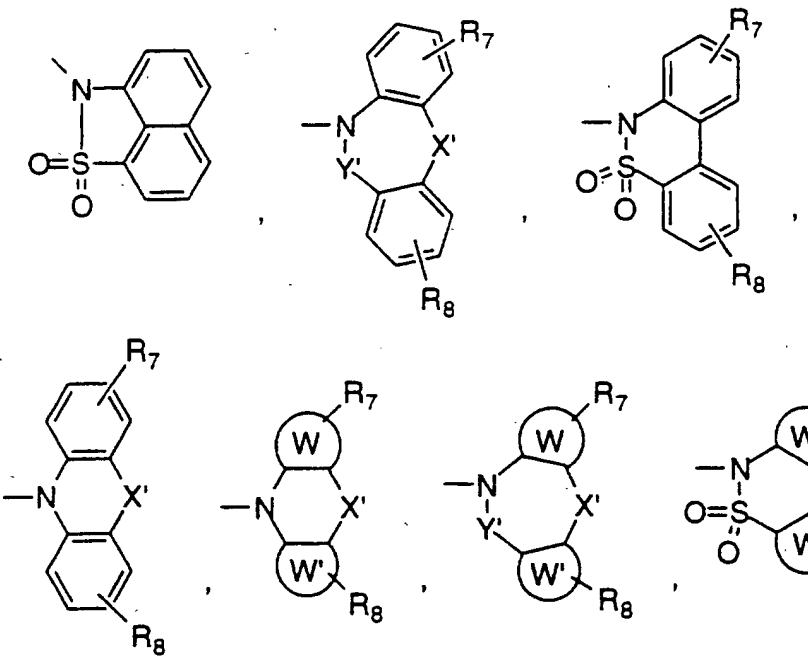
or R_3 and R_4 together with the intervening nitrogen atom represent a piperidine ring which is substituted as depicted in formula (II) :

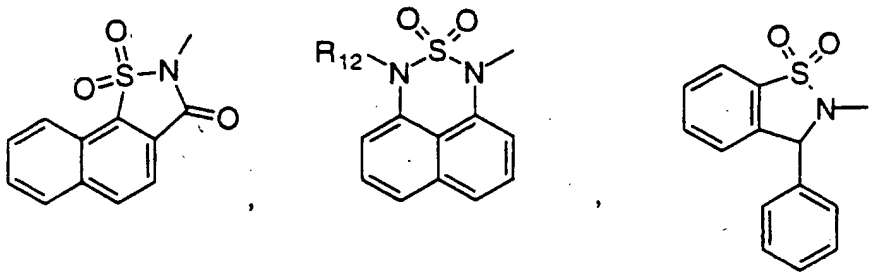


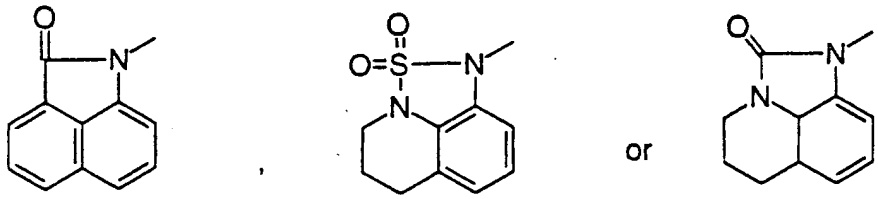
(II)

where R_5 and R_6 represent independently hydrogen or C1-C3 alkyl;

B is a heteroaryl group of formula







or

R_7 and R_8 are independently selected from hydrogen, halo, nitro, C_1-C_6 alkyl optionally substituted with one to three fluorine atoms, hydroxy or C_1-C_6 alkoxy optionally substituted with one to three fluorine atoms.

R_{12} is selected from hydrogen or C_1-C_6 alkyl.

X' represents a single bond, $-CH_2-$, $-CH=CH-$, $-CH_2-CH_2-$, S, $-S-CH_2-$, $-S(O)-$, $-S(O)_2-$, $-S(O)-CH_2-$, $-S(O)_2-CH_2-$, O, $-O-CH_2-$, $N(R_{13})$, $-N(R_{13})-CH_2-$, $-N(R_{13})-S(O)_2-$, C(=O), $-C(=O)-CH_2-$, $-C(=O)-O-$ or $-C(=O)-N(R_{13})-$.

Y' represents $-CH_2-$ or C(=O).

W and W' represent independently a benzene ring or heteroaryl group of 5 to 7 atoms which contains one oxygen atom , one sulfer atom or one or two nitrogen atoms, provided that at least one of W and W' is heteroaryl group.

R_{13} represents hydrogen or C_1-C_6 alkyl.

Particularly preferred compounds of the present invention are those compounds of formula (I) wherein :

When X represents C_3-C_6 cycloalkyl-C_1-C_3-alkyl, adamantyl or C_3-C_6 cycloalkyl, Y represents hydrogen, C_1-C_6 alkyl, C_3-C_6 alkenyl or C_3-C_6 cycloalkyl.

A represents the group $-O-R_9$ in which R_9 represents hydrogen, C_1-C_4 alkyl, C_3-C_6 alkenyl or hydroxy-C_2-C_4-alkyl; or A represents amino, C_1-C_3 alkylamino, phenyl-C_1-C_3-alkylamino, C_3-C_6 alkenylamino, C_2-C_6 dialkylamino, C_4-C_5 cycloalkylamino, C_4-C_7 alkylalkenylamino, piperidino, piperazino, C_1-C_3 alkylpiperazino or morpholino;

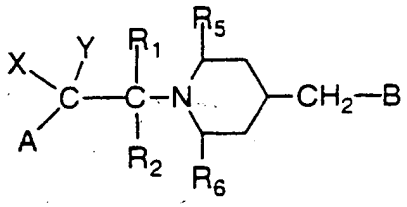
or Y and A taken together may form oxo or hydroxyimino.

R_1 and R_2 which may be the same or different, are hydrogen or C_1-C_3 alkyl.

R_3 represents C_1-C_3 alkyl;

R_4 represents the group $-(CH_2)_p$-B where p is a number selected from 3 to 6;

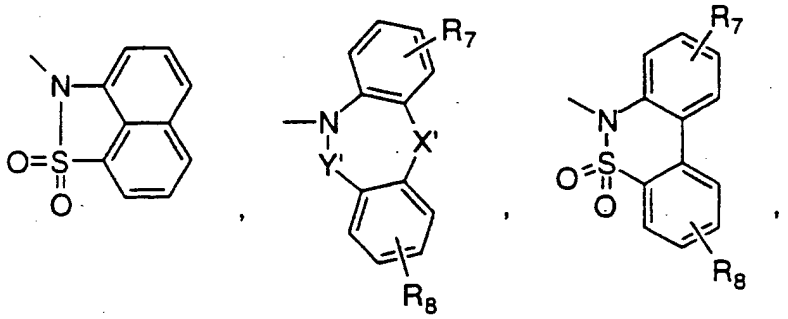
or R_3 and R_4 together with the intervening nitrogen atom represent a piperidine ring which is substituted as depicted in formula (II) :

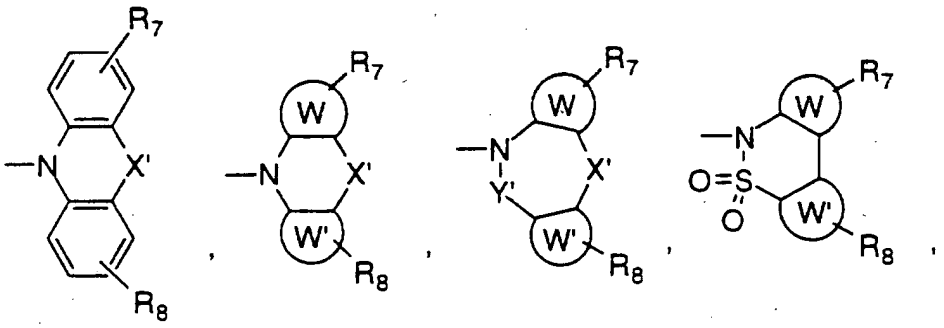


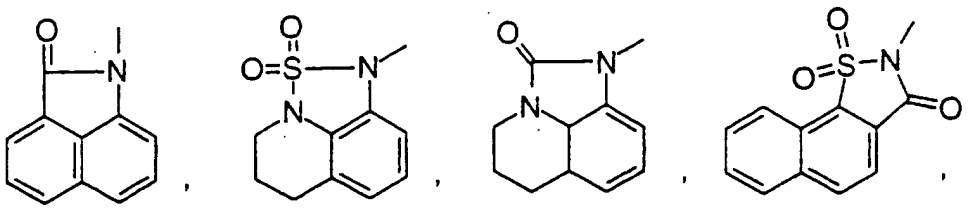
(II)

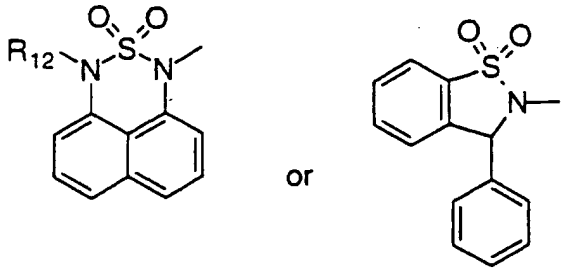
where R_5 and R_6 represent hydrogen;

B is a heteroaryl group of formula









R_7 and R_8 are independently selected from hydrogen, halo, nitro, C_1-C_6 alkyl optionally substituted with one to three fluorine atoms, hydroxy or C_1-C_6 alkoxy optionally substituted with one to three fluorine atoms;

R_{12} is selected from hydrogen or C_1-C_6 alkyl;

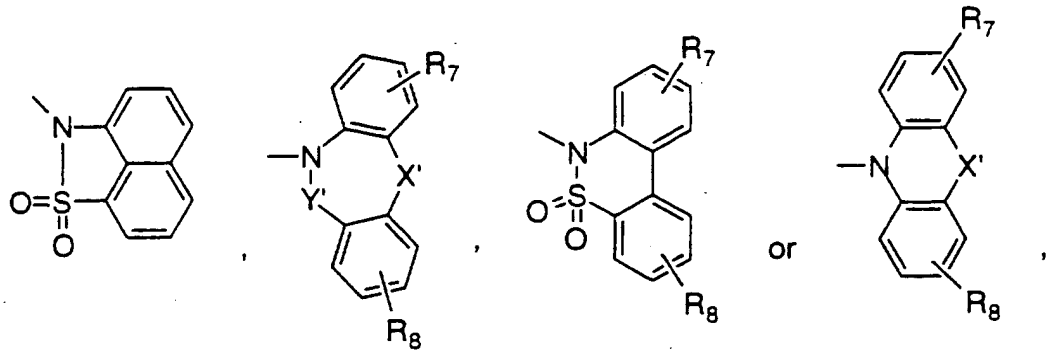
X' represents a single bond, $-CH_2-$, $-CH=CH-$, $-CH_2-CH_2-$, S, $-S-CH_2-$, $-S(O)-$, $-S(O)_2-$, $-S(O)-CH_2-$, $-S(O)_2-CH_2-$, O, $-O-CH_2-$, $N(R_{13})$, $-N(R_{13})-CH_2-$, $-N(R_{13})-S(O)_2-$, C(=O), $-C(=O)-CH_2-$, $-C(=O)-O-$ or $-C(=O)-N(R_{13})-$;

Y' represents $-CH_2-$ or C(=O);

W and W' represent independently a benzene ring or heteroary group of 5 to 7 atoms which contains one oxygen atom, one sulfer atom or one or two nitrogen atoms, provided that at least one of W and W' is heteroaryl group.

R_{13} represents hydrogen or C_1-C_6 alkyl.

Preferable B is



R_7 and R_8 are independently selected from hydrogen, halo, nitro, C_1-C_6 alkyl optionally substituted with one to three fluorine atoms, hydroxy or C_1-C_6 alkoxy optionally substituted with one to three fluorine atoms;

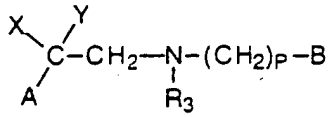
X' represents a single bond, $-CH_2-$, $-CH=CH-$, $-CH_2-CH_2-$, S, $-S-CH_2-$, $-S(O)-$, $-S(O)_2-$, $-S(O)-CH_2-$, $-S(O)_2-CH_2-$, O, $-O-CH_2-$, $N(R_{13})$, $-N(R_{13})-CH_2-$, $-N(R_{13})-S(O)_2-$, C(=O), $-C(=O)-CH_2-$, $-C(=O)-O-$ or $-C(=O)-N(R_{13})-$;

Y' represents $-CH_2-$ or C(=O);

R_{13} represents hydrogen or C_1-C_6 alkyl.

Examples of the compounds of the present invention are set forth in Table I-IV.

TABLE I :



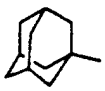
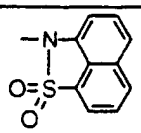
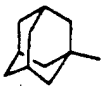
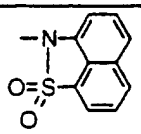
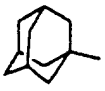
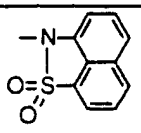
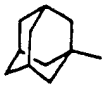
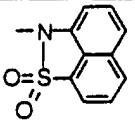
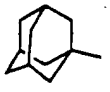
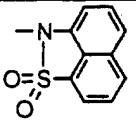
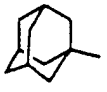
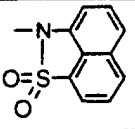
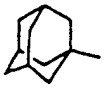
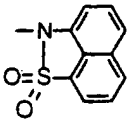
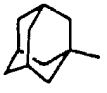
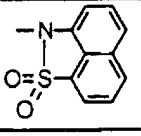
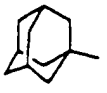
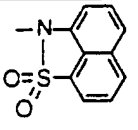
X	Y	A	R_3	P	B
	H	-OH	$-CH_3$	3	
	H	-OH	$-CH_3$	4	
	H	-OH	$-CH_3$	5	
	H	-OH	$-CH_3$	6	
	$-CH_3$	-OH	$-CH_3$	4	
	$-CH_3$	-OH	$-CH_3$	5	
	$-CH_2CH_3$	-OH	$-CH_3$	4	
	$-(CH_2)_2CH_3$	-OH	$-CH_3$	4	
	$-(CH_2)_3CH_3$	-OH	$-CH_3$	4	

TABLE I : (continued)

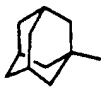
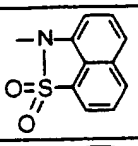
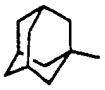
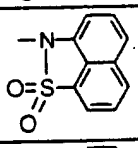
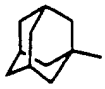
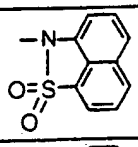
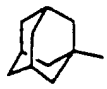
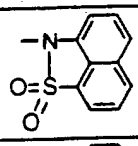
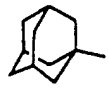
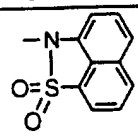
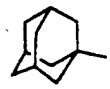
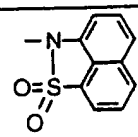
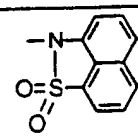
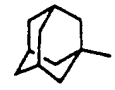
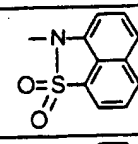
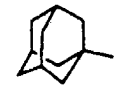
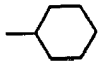
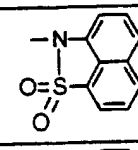
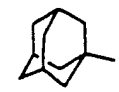
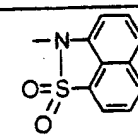
X	Y	A	R_3	P	B
	$-(CH_2)_4CH_3$	-OH	$-CH_3$	4	
	$-(CH_2)_5CH_3$	-OH	$-CH_3$	4	
	$-CH_2CH=CH_2$	-OH	$-CH_3$	4	
	$-(CH_2)_2CH=CH_2$	-OH	$-CH_3$	4	
	$-(CH_2)_3CH=CH_2$	-OH	$-CH_3$	4	
	$-(CH_2)_4CH=CH_2$	-OH	$-CH_3$	4	
		-OH	$-CH_3$	4	
		-OH	$-CH_3$	4	
		-OH	$-CH_3$	4	
	H	-OH	$-CH_2CH_3$	4	

TABLE I : (continued)

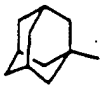
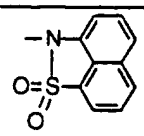
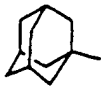
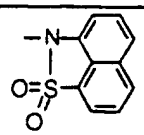
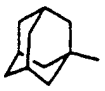
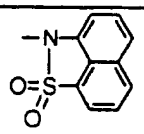
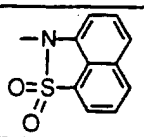
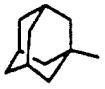
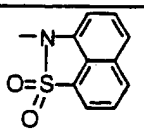
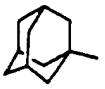
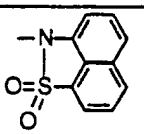
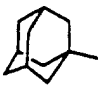
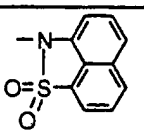
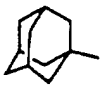
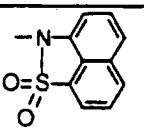
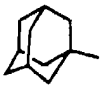
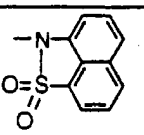
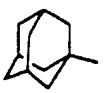
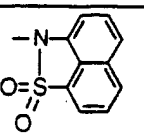
X	Y	A	R_3	P	B
	H	-OH	$-(CH_2)_2CH_3$	4	
	H	-OH	$-CH_2CH=CH_2$	4	
	H	-OH	$-(CH_2)_2CH=CH_2$	4	
	H	-OH	$-(CH_2)_3CH=CH_2$	4	
	H	-OH	$-(CH_2)_4CH=CH_2$	4	
	H	$-OCH_3$	$-CH_3$	4	
	H	$-OCH_2CH_3$	$-CH_3$	4	
	H	$-O(CH_2)_2CH_3$	$-CH_3$	4	
	H	$-O(CH_2)_3CH_3$	$-CH_3$	4	
	H	$-OCH_2CH=CH_2$	$-CH_3$	4	

TABLE I : (continued)

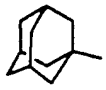
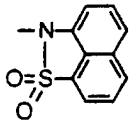
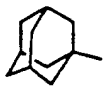
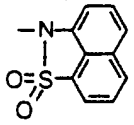
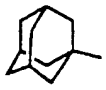
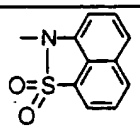
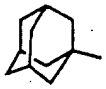
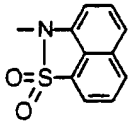
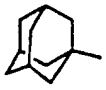
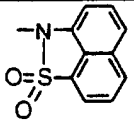
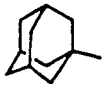
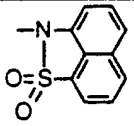
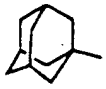
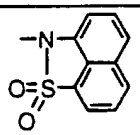
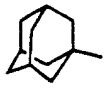
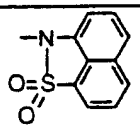
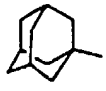
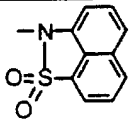
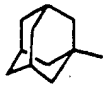
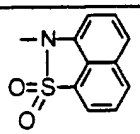
X	Y	A	R_3	P	B
	H	$-O(CH_2)_2CH=CH_2$	$-CH_3$	4	
	H	$-O(CH_2)_3CH=CH_2$	$-CH_3$	4	
	H	$-O(CH_2)_4CH=CH_2$	$-CH_3$	4	
	H	$-O(CH_2)_2OH$	$-CH_3$	4	
	H	$-O(CH_2)_3OH$	$-CH_3$	4	
	H	$-O(CH_2)_4OH$	$-CH_3$	4	
	H	$-NH_2$	$-CH_3$	4	
	H	$-NHCH_3$	$-CH_3$	4	
	H	$-NHCH_2CH_3$	$-CH_3$	4	
	H	$-NH(CH_2)_2CH_3$	$-CH_3$	4	

TABLE I : (continued)

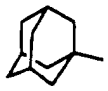
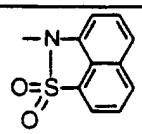
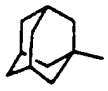
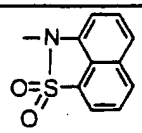
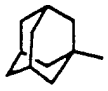
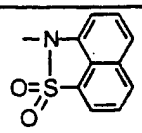
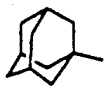
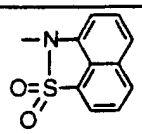
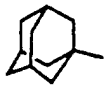
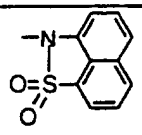
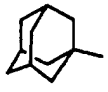
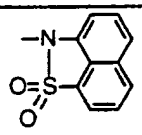
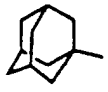
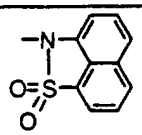
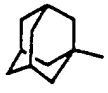
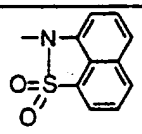
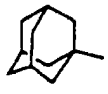
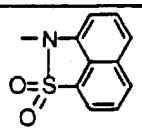
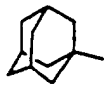
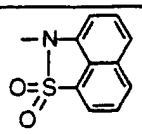
X	Y	A	R_3	P	B
	H	$-NHCH_2-$ 	$-CH_3$	4	
	H	$-NH(CH_2)_2-$ 	$-CH_3$	4	
	H	$-NH(CH_2)_3-$ 	$-CH_3$	4	
	H	$-NHCH_2CH=CH_2$	$-CH_3$	4	
	H	$-NH(CH_2)_2CH=CH_2$	$-CH_3$	4	
	H	$-NH(CH_2)_3CH=CH_2$	$-CH_3$	4	
	H	$-NH(CH_2)_4CH=CH_2$	$-CH_3$	4	
	H	$-N(CH_3)_2$	$-CH_3$	4	
	H	$-N(CH_3)CH_2CH_3$	$-CH_3$	4	
	H	$-N(CH_2CH_3)_2$	$-CH_3$	4	

TABLE I : (continued)

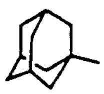
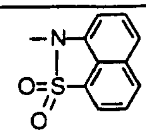
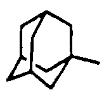
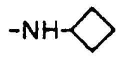
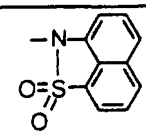
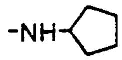
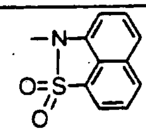
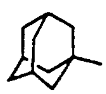
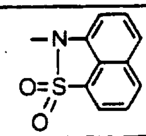
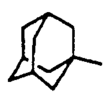
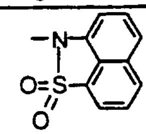
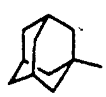
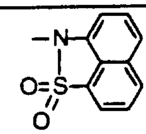
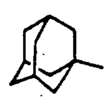
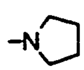
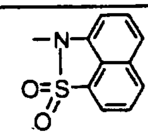
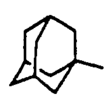
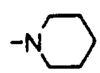
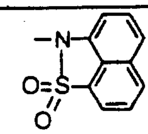
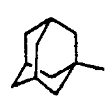
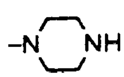
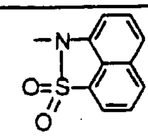
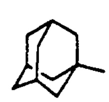
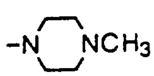
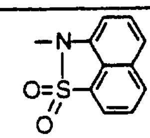
X	Y	A	R_3	P	B
	H	$-N(CH_2CH_2CH_3)_2$	$-CH_3$	4	
	H		$-CH_3$	4	
	H		$-CH_3$	4	
	H	$-N(CH_3)CH_2CH=CH_2$	$-CH_3$	4	
	H	$-N(CH_2CH_3)CH_2CH=CH_2$	$-CH_3$	4	
	H	$-N(CH_2CH_2CH_3)(CH_2)_2CH=CH_2$	$-CH_3$	4	
	H		$-CH_3$	4	
	H		$-CH_3$	4	
	H		$-CH_3$	4	
	H		$-CH_3$	4	

TABLE I : (continued)

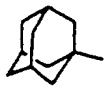
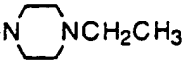
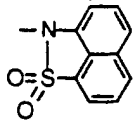
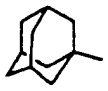
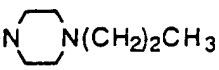
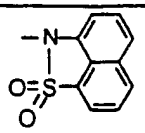
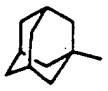
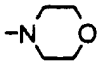
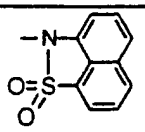
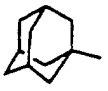
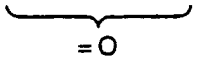
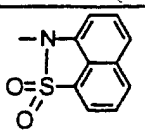
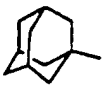
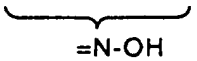
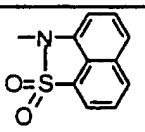
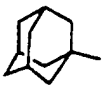
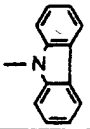
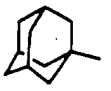
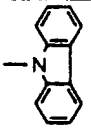
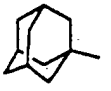
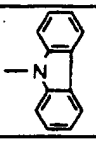
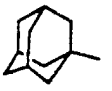
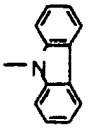
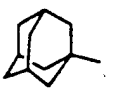
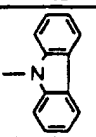
X	Y	A	R_3	P	B
	H		$-CH_3$	4	
	H		$-CH_3$	4	
	H		$-CH_3$	4	
			$-CH_3$	4	
			$-CH_3$	4	
	H	-OH	$-CH_3$	4	
	H	$-OCH_3$	$-CH_3$	4	
	H	$-OCH_2CH_3$	$-CH_3$	4	
	H	$-O(CH_2)_2CH_3$	$-CH_3$	4	
	H	$-OCH_2CH=CH_2$	$-CH_3$	4	

TABLE I : (continued)

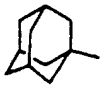
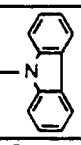
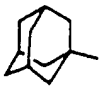
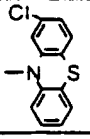
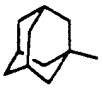
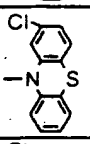
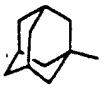
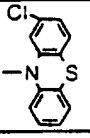
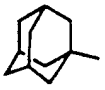
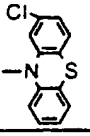
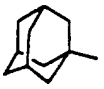
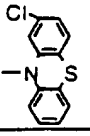
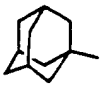
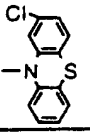
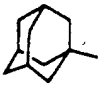
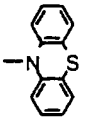
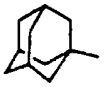
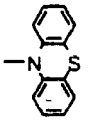
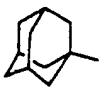
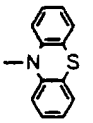
X	Y	A	R_3	P	B
	H	$-O(CH_2)_2OH$	$-CH_3$	4	
	H	-OH	$-CH_3$	4	
	H	$-OCH_3$	$-CH_3$	4	
	H	$-OCH_2CH_3$	$-CH_3$	4	
	H	$-O(CH_2)_2CH_3$	$-CH_3$	4	
	H	$-OCH_2CH=CH_2$	$-CH_3$	4	
	H	$-O(CH_2)_2OH$	$-CH_3$	4	
	H	-OH	$-CH_3$	4	
	H	$-OCH_3$	$-CH_3$	4	
	H	$-OCH_2CH_3$	$-CH_3$	4	

TABLE I : (continued)

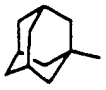
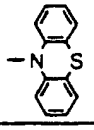
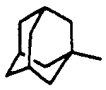
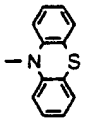
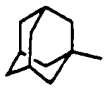
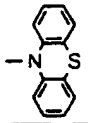
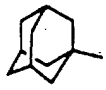
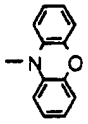
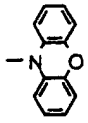
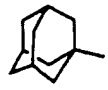
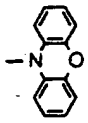
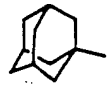
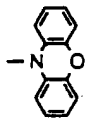
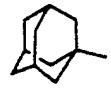
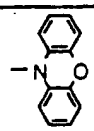
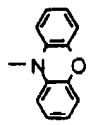
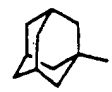
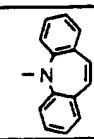
X	Y	A	R_3	P	B
	H	$-O(CH_2)_2CH_3$	$-CH_3$	4	
	H	$-OCH_2CH=CH_2$	$-CH_3$	4	
	H	$-O(CH_2)_2OH$	$-CH_3$	4	
	H	$-OH$	$-CH_3$	4	
	H	$-OCH_3$	$-CH_3$	4	
	H	$-OCH_2CH_3$	$-CH_3$	4	
	H	$-O(CH_2)_2CH_3$	$-CH_3$	4	
	H	$-OCH_2CH=CH_2$	$-CH_3$	4	
	H	$-O(CH_2)_2OH$	$-CH_3$	4	
	H	$-OH$	$-CH_3$	4	

TABLE I : (continued)

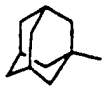
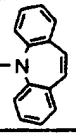
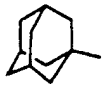
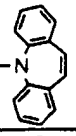
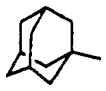
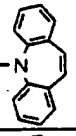
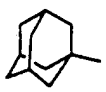
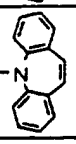
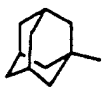
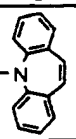
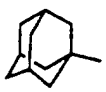
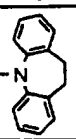
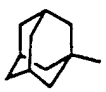
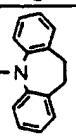
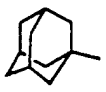
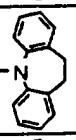
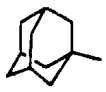
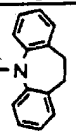
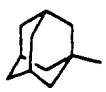
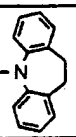
X	Y	A	R_3	P	B
	H	$-OCH_3$	$-CH_3$	4	
	H	$-OCH_2CH_3$	$-CH_3$	4	
	H	$-O(CH_2)_2CH_3$	$-CH_3$	4	
	H	$-OCH_2CH=CH_2$	$-CH_3$	4	
	H	$-O(CH_2)_2OH$	$-CH_3$	4	
	H	$-OH$	$-CH_3$	4	
	H	$-OCH_3$	$-CH_3$	4	
	H	$-OCH_2CH_3$	$-CH_3$	4	
	H	$-O(CH_2)_2CH_3$	$-CH_3$	4	
	H	$-OCH_2CH=CH_2$	$-CH_3$	4	

TABLE I : (continued)

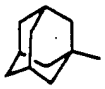
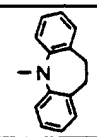
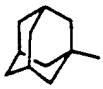
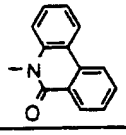
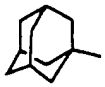
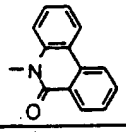
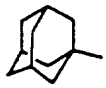
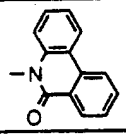
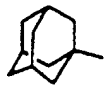
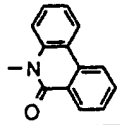
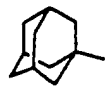
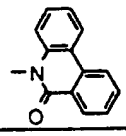
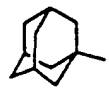
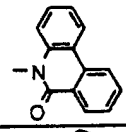
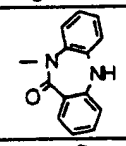
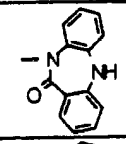
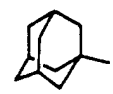
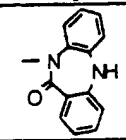
X	Y	A	R_3	P	B
	H	$-O(CH_2)_2OH$	$-CH_3$	4	
	H	-OH	$-CH_3$	4	
	H	$-OCH_3$	$-CH_3$	4	
	H	$-OCH_2CH_3$	$-CH_3$	4	
	H	$-O(CH_2)_2CH_3$	$-CH_3$	4	
	H	$-OCH_2CH=CH_2$	$-CH_3$	4	
	H	$-O(CH_2)_2OH$	$-CH_3$	4	
	H	-OH	$-CH_3$	4	
	H	$-OCH_3$	$-CH_3$	4	
	H	$-OCH_2CH_3$	$-CH_3$	4	

TABLE I: (continued)

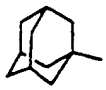
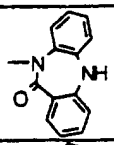
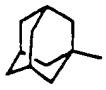
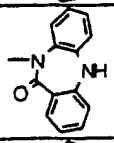
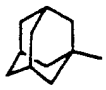
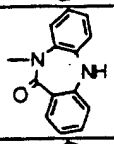
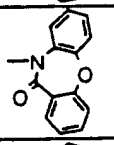
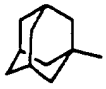
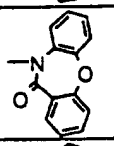
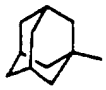
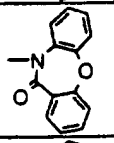
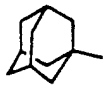
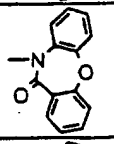
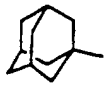
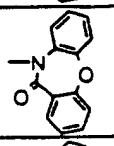
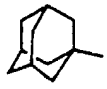
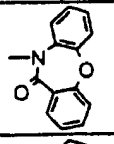
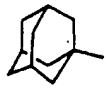
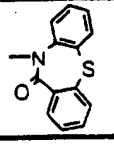
X	Y	A	R_3	P	B
	H	$-O(CH_2)_2CH_3$	$-CH_3$	4	
	H	$-OCH_2CH=CH_2$	$-CH_3$	4	
	H	$-O(CH_2)_2OH$	$-CH_3$	4	
	H	$-OH$	$-CH_3$	4	
	H	$-OCH_3$	$-CH_3$	4	
	H	$-OCH_2CH_3$	$-CH_3$	4	
	H	$-O(CH_2)_2CH_3$	$-CH_3$	4	
	H	$-OCH_2CH=CH_2$	$-CH_3$	4	
	H	$-O(CH_2)_2OH$	$-CH_3$	4	
	H	$-OH$	$-CH_3$	4	

TABLE I : (continued)

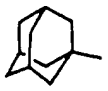
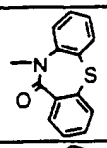
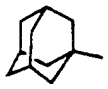
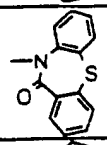
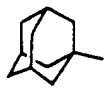
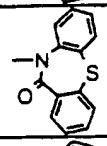
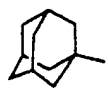
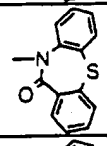
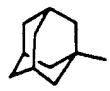
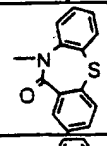
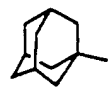
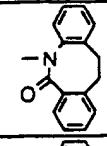
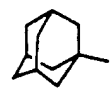
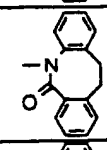
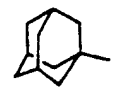
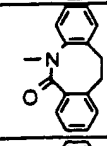
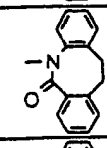
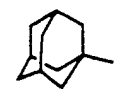
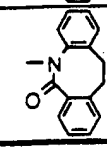
X	Y	A	R_3	P	B
	H	$-OCH_3$	$-CH_3$	4	
	H	$-OCH_2CH_3$	$-CH_3$	4	
	H	$-O(CH_2)_2CH_3$	$-CH_3$	4	
	H	$-OCH_2CH=CH_2$	$-CH_3$	4	
	H	$-O(CH_2)_2OH$	$-CH_3$	4	
	H	$-OH$	$-CH_3$	4	
	H	$-OCH_3$	$-CH_3$	4	
	H	$-OCH_2CH_3$	$-CH_3$	4	
	H	$-O(CH_2)_2CH_3$	$-CH_3$	4	
	H	$-OCH_2CH=CH_2$	$-CH_3$	4	

TABLE 1 : (continued)

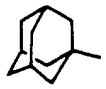
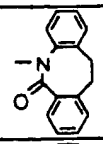
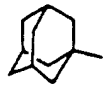
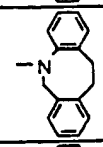
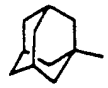
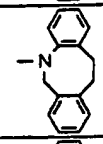
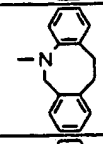
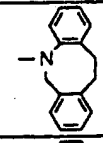
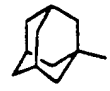
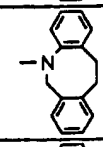
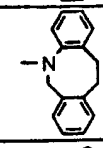
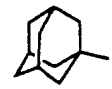
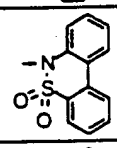
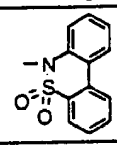
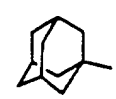
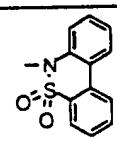
X	Y	A	R_3	P	B
	H	$-O(CH_2)_2OH$	$-CH_3$	4	
	H	$-OH$	$-CH_3$	4	
	H	$-OCH_3$	$-CH_3$	4	
	H	$-OCH_2CH_3$	$-CH_3$	4	
	H	$-O(CH_2)_2CH_3$	$-CH_3$	4	
	H	$-OCH_2CH=CH_2$	$-CH_3$	4	
	H	$-O(CH_2)_2OH$	$-CH_3$	4	
	H	$-OH$	$-CH_3$	4	
	H	$-OCH_3$	$-CH_3$	4	
	H	$-OCH_2CH_3$	$-CH_3$	4	

TABLE I : (continued)

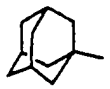
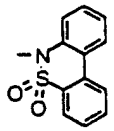
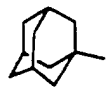
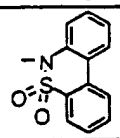
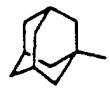
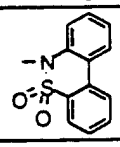
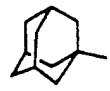
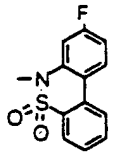
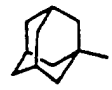
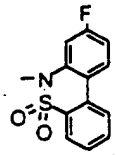
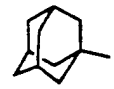
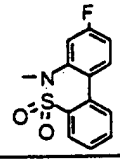
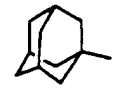
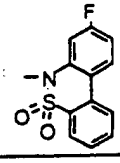
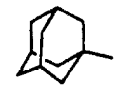
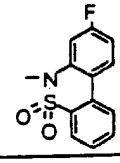
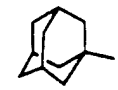
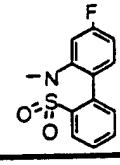
X	Y	A	R_3	P	B
	H	$-O(CH_2)_2CH_3$	$-CH_3$	4	
	H	$-OCH_2CH=CH_2$	$-CH_3$	4	
	H	$-O(CH_2)_2OH$	$-CH_3$	4	
	H	-OH	$-CH_3$	4	
	H	$-OCH_3$	$-CH_3$	4	
	H	$-OCH_2CH_3$	$-CH_3$	4	
	H	$-O(CH_2)_2CH_3$	$-CH_3$	4	
	H	$-OCH_2CH=CH_2$	$-CH_3$	4	
	H	$-O(CH_2)_2OH$	$-CH_3$	4	

TABLE I : (continued)

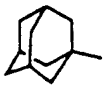
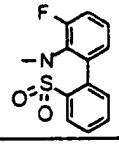
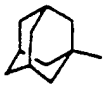
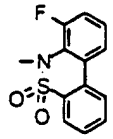
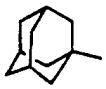
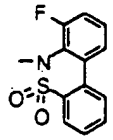
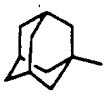
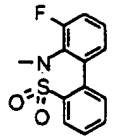
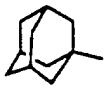
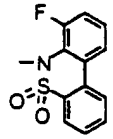
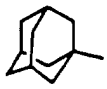
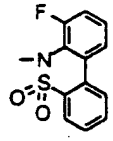
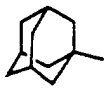
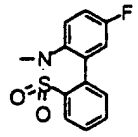
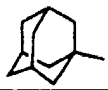
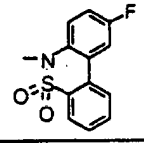
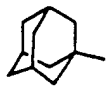
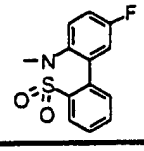
X	Y	A	R_3	P	B
	H	-OH	$-CH_3$	4	
	H	$-OCH_3$	$-CH_3$	4	
	H	$-OCH_2CH_3$	$-CH_3$	4	
	H	$-O(CH_2)_2CH_3$	$-CH_3$	4	
	H	$-OCH_2CH=CH_2$	$-CH_3$	4	
	H	$-O(CH_2)_2OH$	$-CH_3$	4	
	H	-OH	$-CH_3$	4	
	H	$-OCH_3$	$-CH_3$	4	
	H	$-OCH_2CH_3$	$-CH_3$	4	

TABLE I : (continued)

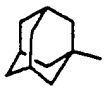
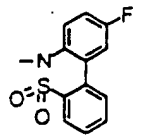
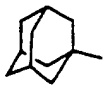
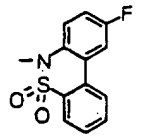
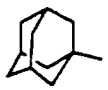
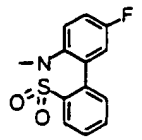
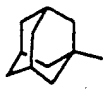
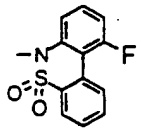
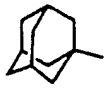
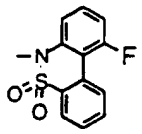
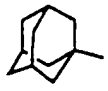
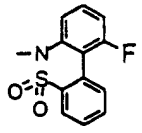
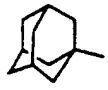
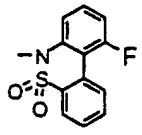
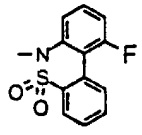
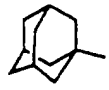
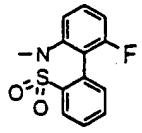
X	Y	A	R_3	P	B
	H	$-O(CH_2)_2CH_3$	$-CH_3$	4	
	H	$-OCH_2CH=CH_2$	$-CH_3$	4	
	H	$-O(CH_2)_2OH$	$-CH_3$	4	
	H	$-OH$	$-CH_3$	4	
	H	$-OCH_3$	$-CH_3$	4	
	H	$-OCH_2CH_3$	$-CH_3$	4	
	H	$-O(CH_2)_2CH_3$	$-CH_3$	4	
	H	$-OCH_2CH=CH_2$	$-CH_3$	4	
	H	$-O(CH_2)_2OH$	$-CH_3$	4	

TABLE I : (continued)

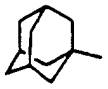
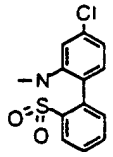
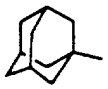
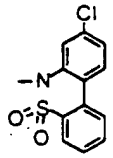
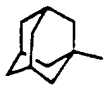
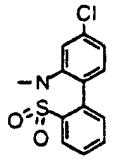
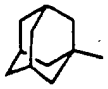
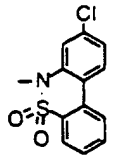
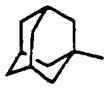
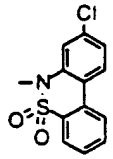
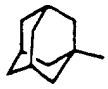
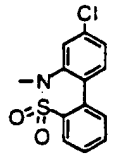
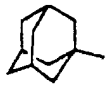
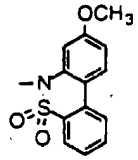
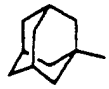
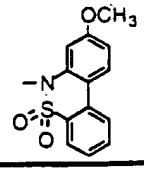
X	Y	A	R_3	P	B
	H	-OH	$-CH_3$	4	
	H	$-OCH_3$	$-CH_3$	4	
	H	$-OCH_2CH_3$	$-CH_3$	4	
	H	$-O(CH_2)_2CH_3$	$-CH_3$	4	
	H	$-OCH_2CH=CH_2$	$-CH_3$	4	
	H	$-O(CH_2)_2OH$	$-CH_3$	4	
	H	-OH	$-CH_3$	4	
	H	$-OCH_3$	$-CH_3$	4	

TABLE I : (continued)

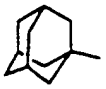
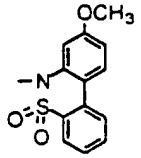
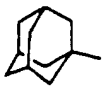
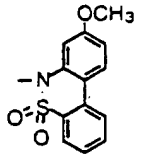
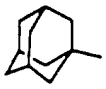
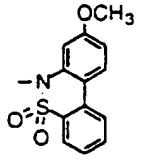
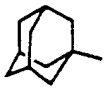
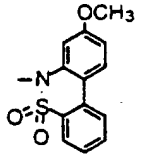
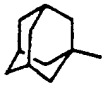
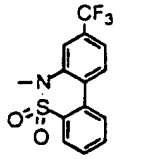
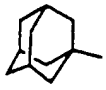
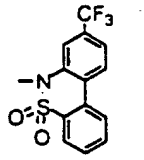
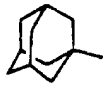
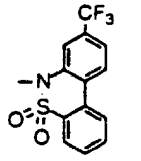
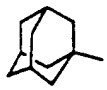
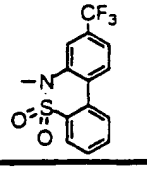
X	Y	A	R_3	P	B
	H	$-OCH_2CH_3$	$-CH_3$	4	
	H	$-O(CH_2)_2CH_3$	$-CH_3$	4	
	H	$-OCH_2CH=CH_2$	$-CH_3$	4	
	H	$-O(CH_2)_2OH$	$-CH_3$	4	
	H	-OH	$-CH_3$	4	
	H	$-OCH_3$	$-CH_3$	4	
	H	$-OCH_2CH_3$	$-CH_3$	4	
	H	$-O(CH_2)_2CH_3$	$-CH_3$	4	

TABLE I: (continued)

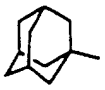
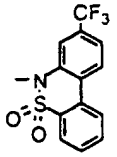
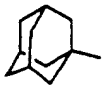
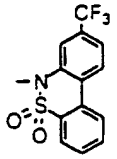
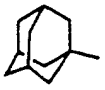
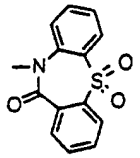
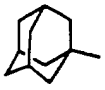
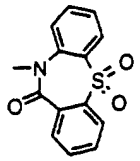
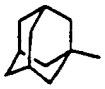
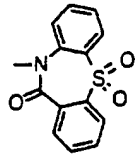
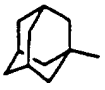
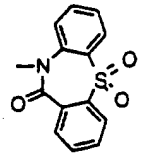
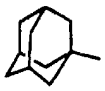
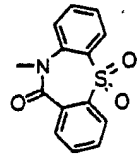
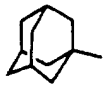
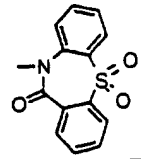
X	Y	A	R_3	P	B
	H	$-OCH_2CH=CH_2$	$-CH_3$	4	
	H	$-O(CH_2)_2OH$	$-CH_3$	4	
	H	-OH	$-CH_3$	4	
	H	$-OCH_3$	$-CH_3$	4	
	H	$-OCH_2CH_3$	$-CH_3$	4	
	H	$-O(CH_2)_2CH_3$	$-CH_3$	4	
	H	$-OCH_2CH=CH_2$	$-CH_3$	4	
	H	$-O(CH_2)_2OH$	$-CH_3$	4	

TABLE I : (continued)

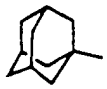
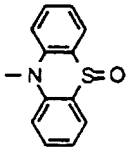
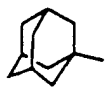
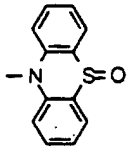
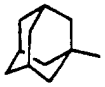
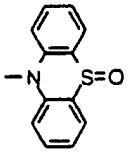
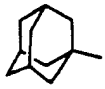
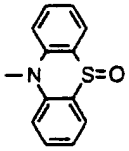
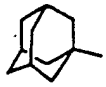
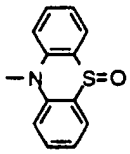
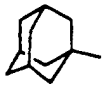
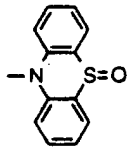
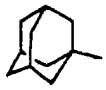
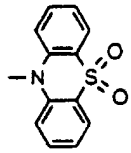
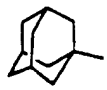
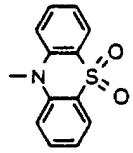
X	Y	A	R_3	P	B
	H	-OH	$-CH_3$	4	
	H	$-OCH_3$	$-CH_3$	4	
	H	$-OCH_2CH_3$	$-CH_3$	4	
	H	$-O(CH_2)_2CH_3$	$-CH_3$	4	
	H	$-OCH_2CH=CH_2$	$-CH_3$	4	
	H	$-O(CH_2)_2OH$	$-CH_3$	4	
	H	-OH	$-CH_3$	4	
	H	$-OCH_3$	$-CH_3$	4	

TABLE I : (continued)

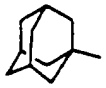
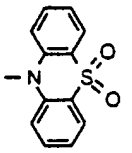
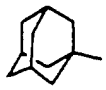
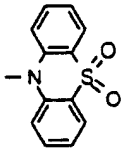
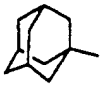
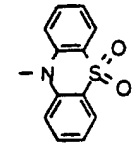
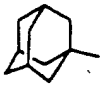
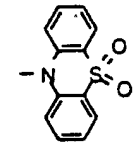
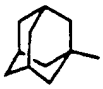
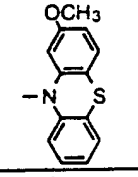
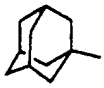
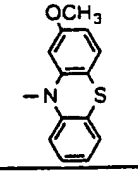
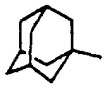
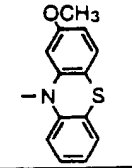
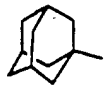
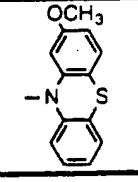
X	Y	A	R_3	P	B
	H	$-OCH_2CH_3$	$-CH_3$	4	
	H	$-O(CH_2)_2CH_3$	$-CH_3$	4	
	H	$-OCH_2CH=CH_2$	$-CH_3$	4	
	H	$-O(CH_2)_2OH$	$-CH_3$	4	
	H	-OH	$-CH_3$	4	
	H	$-OCH_3$	$-CH_3$	4	
	H	$-OCH_2CH_3$	$-CH_3$	4	
	H	$-O(CH_2)_2CH_3$	$-CH_3$	4	

TABLE I : (continued)

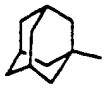
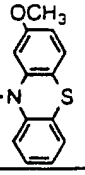
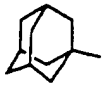
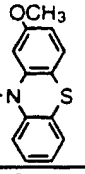
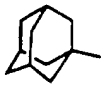
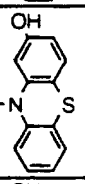
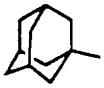
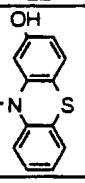
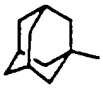
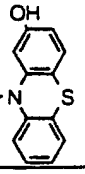
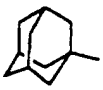
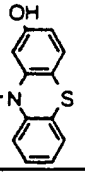
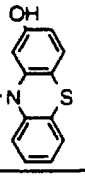
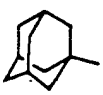
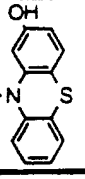
X	Y	A	R_3	P	B
	H	$-OCH_2CH=CH_2$	$-CH_3$	4	
	H	$-O(CH_2)_2OH$	$-CH_3$	4	
	H	$-OH$	$-CH_3$	4	
	H	$-OCH_3$	$-CH_3$	4	
	H	$-OCH_2CH_3$	$-CH_3$	4	
	H	$-O(CH_2)_2CH_3$	$-CH_3$	4	
	H	$-OCH_2CH=CH_2$	$-CH_3$	4	
	H	$-O(CH_2)_2OH$	$-CH_3$	4	

TABLE I : (continued)

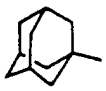
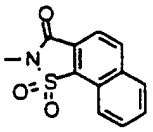
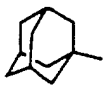
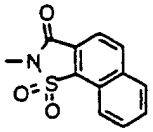
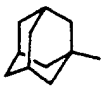
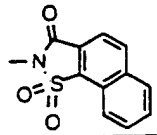
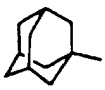
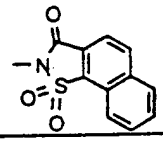
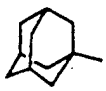
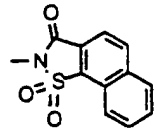
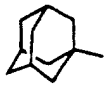
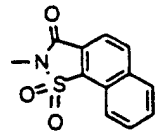
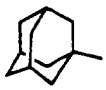
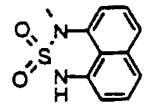
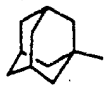
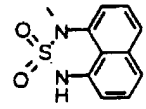
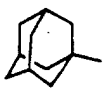
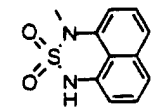
X	Y	A	R_3	P	B
	H	-OH	$-CH_3$	4	
	H	$-OCH_3$	$-CH_3$	4	
	H	$-OCH_2CH_3$	$-CH_3$	4	
	H	$-O(CH_2)_2CH_3$	$-CH_3$	4	
	H	$-OCH_2CH=CH_2$	$-CH_3$	4	
	H	$-O(CH_2)_2OH$	$-CH_3$	4	
	H	-OH	$-CH_3$	4	
	H	$-OCH_3$	$-CH_3$	4	
	H	$-OCH_2CH_3$	$-CH_3$	4	

TABLE I : (continued)

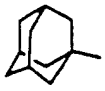
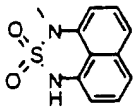
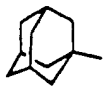
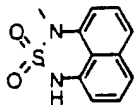
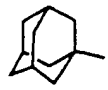
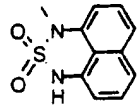
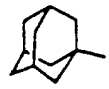
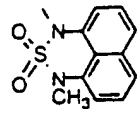
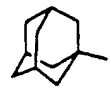
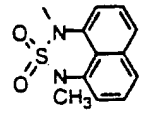
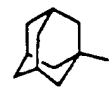
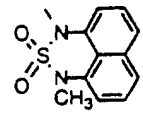
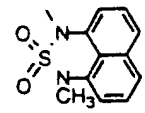
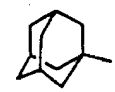
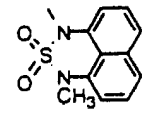
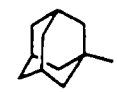
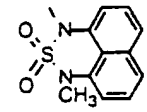
X	Y	A	R_3	P	B
	H	$-O(CH_2)_2CH_3$	$-CH_3$	4	
	H	$-OCH_2CH=CH_2$	$-CH_3$	4 4	
	H	$-O(CH_2)_2OH$	$-CH_3$		
	H	$-OH$	$-CH_3$	4	
	H	$-OCH_3$	$-CH_3$	4	
	H	$-OCH_2CH_3$	$-CH_3$	4	
	H	$-O(CH_2)_2CH_3$	$-CH_3$	4	
	H	$-OCH_2CH=CH_2$	$-CH_3$	4	
	H	$-O(CH_2)_2OH$	$-CH_3$	4	

TABLE I : (continued)

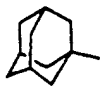
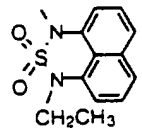
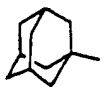
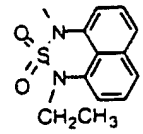
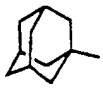
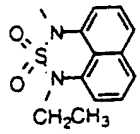
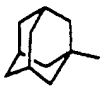
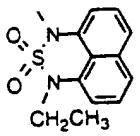
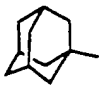
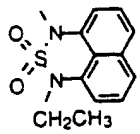
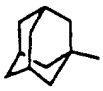
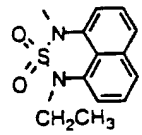
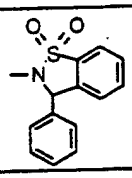
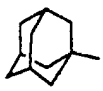
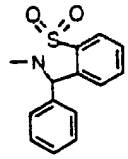
X	Y	A	R_3	P	B
	H	-OH	$-CH_3$	4	
	H	$-OCH_3$	$-CH_3$	4	
	H	$-OCH_2CH_3$	$-CH_3$	4	
	H	$-O(CH_2)_2CH_3$	$-CH_3$	4	
	H	$-OCH_2CH=CH_2$	$-CH_3$	4	
	H	$-O(CH_2)_2OH$	$-CH_3$	4	
	H	-OH	$-CH_3$	4	
	H	$-OCH_3$	$-CH_3$	4	

TABLE I : (continued)

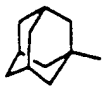
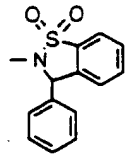
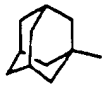
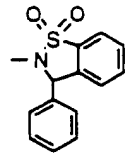
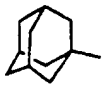
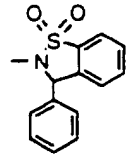
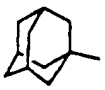
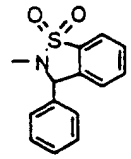
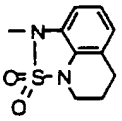
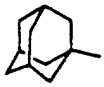
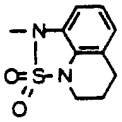
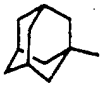
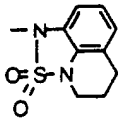
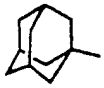
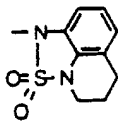
X	Y	A	R_3	P	B
	H	$-OCH_2CH_3$	$-CH_3$	4	
	H	$-O(CH_2)_2CH_3$	$-CH_3$	4	
	H	$-OCH_2CH=CH_2$	$-CH_3$	4	
	H	$-O(CH_2)_2OH$	$-CH_3$	4	
	H	-OH	$-CH_3$	4	
	H	$-OCH_3$	$-CH_3$	4	
	H	$-OCH_2CH_3$	$-CH_3$	4	
	H	$-O(CH_2)_2CH_3$	$-CH_3$	4	

TABLE I : (continued)

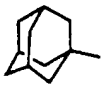
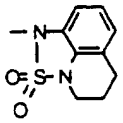
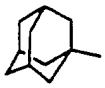
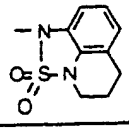
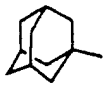
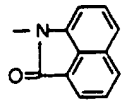
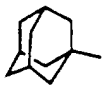
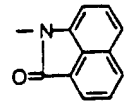
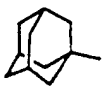
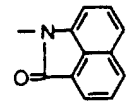
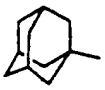
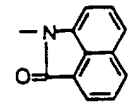
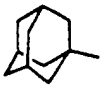
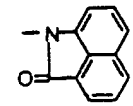
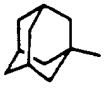
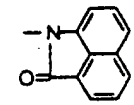
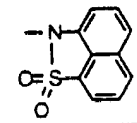
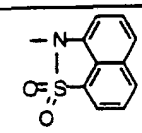
X	Y	A	R_3	P	B
	H	$-OCH_2CH=CH_2$	$-CH_3$	4	
	H	$-O(CH_2)_2OH$	$-CH_3$	4	
	H	-OH	$-CH_3$	4	
	H	$-OCH_3$	$-CH_3$	4	
	H	$-OCH_2CH_3$	$-CH_3$	4	
	H	$-O(CH_2)_2CH_3$	$-CH_3$	4	
	H	$-OCH_2CH=CH_2$	$-CH_3$	4	
	H	$-O(CH_2)_2OH$	$-CH_3$	4	
	H	-OH	$-CH_3$	4	
	H	$-OCH_3$	$-CH_3$	4	

TABLE I : (continued)

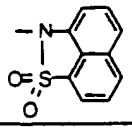
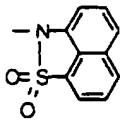
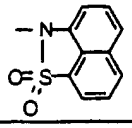
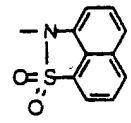
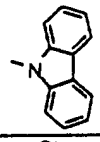
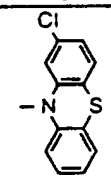
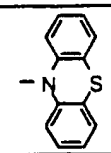
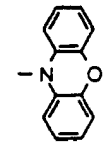
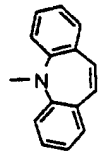
X	Y	A	R_3	P	B
	H	$-OCH_2CH_3$	$-CH_3$	4	
	H	$-O(CH_2)_2CH_3$	$-CH_3$	4	
	H	$-OCH_2CH=CH_2$	$-CH_3$	4	
	H	$-O(CH_2)OH$	$-CH_3$	4	
	H	-OH	$-CH_3$	4	
	H	-OH	$-CH_3$	4	
	H	-OH	$-CH_3$	4	
	H	-OH	$-CH_3$	4	
	H	-OH	$-CH_3$	4	

TABLE I : (continued)

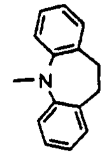
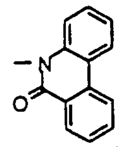
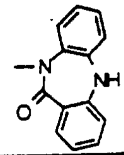
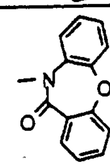
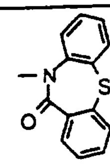
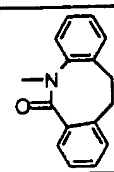
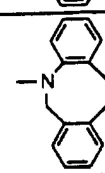
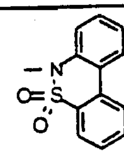
X	Y	A	R_3	P	B
	H	-OH	$-CH_3$	4	
	H	-OH	$-CH_3$	4	
	H	-OH	$-CH_3$	4	
	H	-OH	$-CH_3$	4	
	H	-OH	$-CH_3$	4	
	H	-OH	$-CH_3$	4	
	H	-OH	$-CH_3$	4	
	H	-OH	$-CH_3$	4	

TABLE I : (continued)

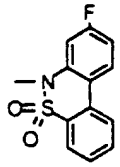
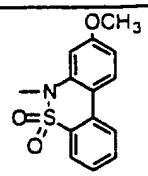
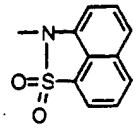
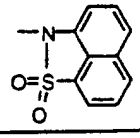
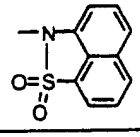
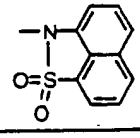
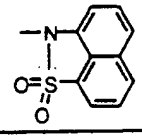
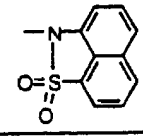
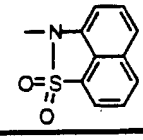
X	Y	A	R_3	P	B
	H	-OH	$-CH_3$	4	
	H	-OH	$-CH_3$	4	
	$-CH_3$	-OH	$-CH_3$	4	
	$-CH_2CH_3$	-OH	$-CH_3$	4	
	$-(CH_2)_2CH_3$	-OH	$-CH_3$	4	
	$-(CH_2)_5CH_3$	-OH	$-CH_3$	4	
	$-CH_2CH=CH_2$	-OH	$-CH_3$	4	
	$-(CH_2)_4CH=CH_2$	-OH	$-CH_3$	4	
		-OH	$-CH_3$	4	

TABLE I: (continued)

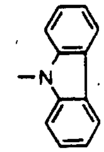
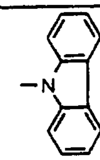
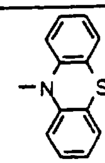
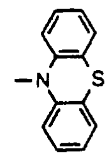
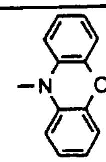
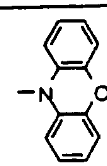
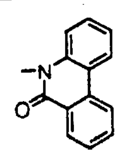
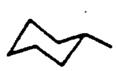
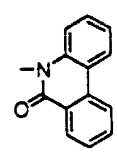
X	Y	A	R_3	P	B
	$-CH_3$	-OH	$-CH_3$	4	
	$-CH_2CH_3$	-OH	$-CH_3$	4	
	$-CH_3$	-OH	$-CH_3$	4	
	$-CH_2CH_3$	-OH	$-CH_3$	4	
	$-CH_3$	-OH	$-CH_3$	4	
	$-CH_2CH_3$	-OH	$-CH_3$	4	
	$-CH_3$	-OH	$-CH_3$	4	
	$-CH_2CH_3$	-OH	$-CH_3$	4	

TABLE I : (continued)

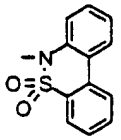
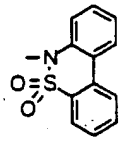
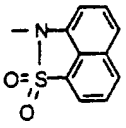
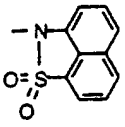
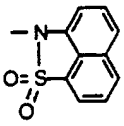
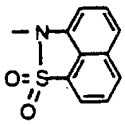
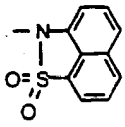
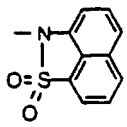
X	Y	A	R_3	P	B
	$-CH_3$	-OH	$-CH_3$	4	
	$-CH_2CH_3$	-OH	$-CH_3$	4	
	H	-OH	$-CH_3$	4	
	H	$-OCH_3$	$-CH_3$	4	
	H	$-OCH_2CH_3$	$-CH_3$	4	
	H	$-O(CH_2)_2CH_3$	$-CH_3$	4	
	H	$-OCH_2CH=CH_2$	$-CH_3$	4	
	H	$-O(CH_2)_2OH$	$-CH_3$	4	

TABLE I : (continued)

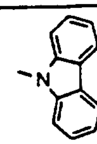
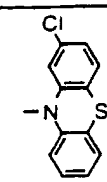
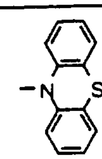
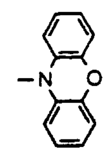
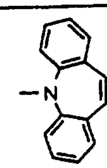
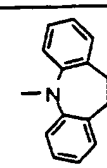
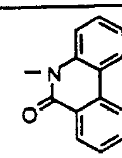
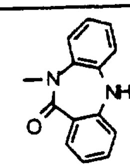
X	Y	A	R_3	P	B
	H	-OH	$-CH_3$	4	
	H	-OH	$-CH_3$	4	
	H	-OH	$-CH_3$	4	
	H	-OH	$-CH_3$	4	
	H	-OH	$-CH_3$	4	
	H	-OH	$-CH_3$	4	
	H	-OH	$-CH_3$	4	
	H	-OH	$-CH_3$	4	

TABLE I : (continued)

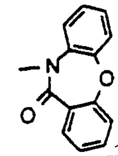
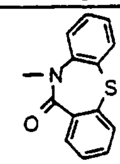
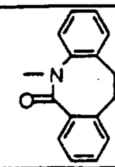
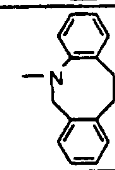
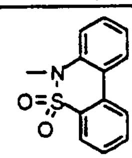
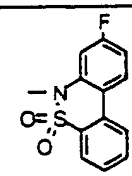
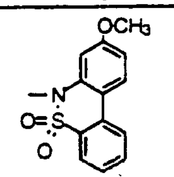
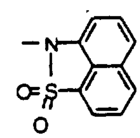
X	Y	A	R_3	P	B
	H	-OH	$-CH_3$	4	
	H	-OH	$-CH_3$	4	
	H	-OH	$-CH_3$	4	
	H	-OH	$-CH_3$	4	
	H	-OH	$-CH_3$	4	
	H	-OH	$-CH_3$	4	
	H	-OH	$-CH_3$	4	
	$-CH_3$	-OH	$-CH_3$	4	

TABLE I : (continued)

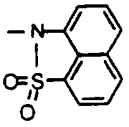
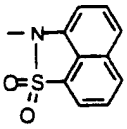
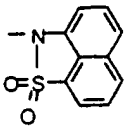
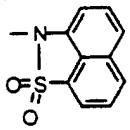
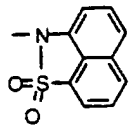
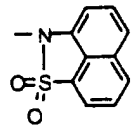
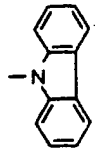
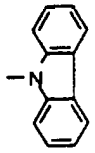
X	Y	A	R_3	P	B
	$-CH_2CH_3$	-OH	$-CH_3$	4	
	$-(CH_2)_2CH_3$	-OH	$-CH_3$	4	
	$-(CH_2)_5CH_3$	-OH	$-CH_3$	4	
	$-CH_2CH=CH_2$	-OH	$-CH_3$	4	
	$-(CH_2)_4CH=CH_2$	-OH	$-CH_3$	4	
		-OH	$-CH_3$	4	
	$-CH_3$	-OH	$-CH_3$	4	
	$-CH_2CH_3$	-OH	$-CH_3$	4	

TABLE I: (continued)

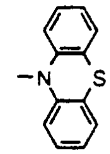
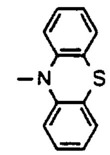
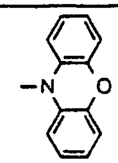
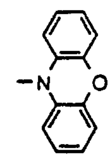
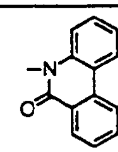
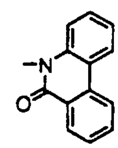
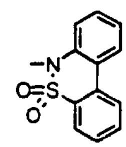
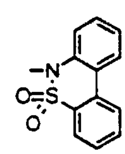
X	Y	A	R_3	P	B
	$-CH_3$	-OH	$-CH_3$	4	
	$-CH_2CH_3$	-OH	$-CH_3$	4	
	$-CH_3$	-OH	$-CH_3$	4	
	$-CH_2CH_3$	-OH	$-CH_3$	4	
	$-CH_3$	-OH	$-CH_3$	4	
	$-CH_2CH_3$	-OH	$-CH_3$	4	
	$-CH_3$	-OH	$-CH_3$	4	
	$-CH_2CH_3$	-OH	$-CH_3$	4	

TABLE I : (continued)

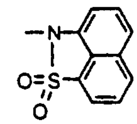
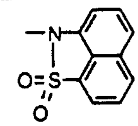
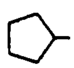
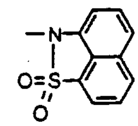
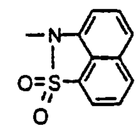
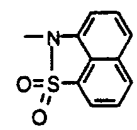
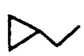
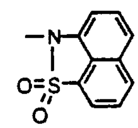
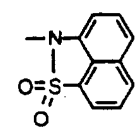
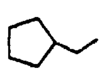
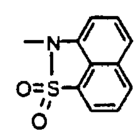
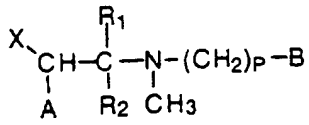
X	Y	A	R_3	P	B
	H	-OH	$-CH_3$	4	
	H	-OH	$-CH_3$	4	
	H	-OH	$-CH_3$	4	
	H	-OH	$-CH_3$	4	
	H	-OH	$-CH_3$	4	
	H	-OH	$-CH_3$	4	
	H	-OH	$-CH_3$	4	
	H	-OH	$-CH_3$	4	

TABLE II



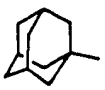
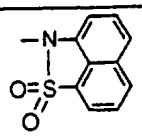
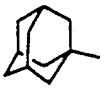
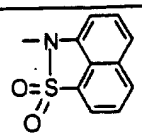
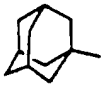
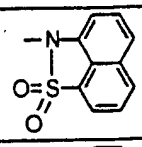
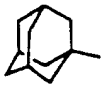
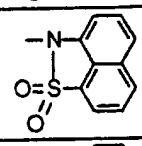
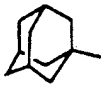
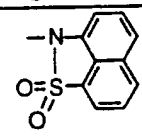
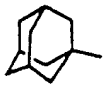
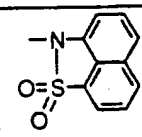
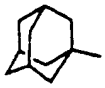
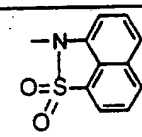
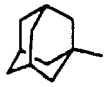
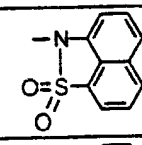
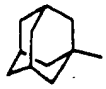
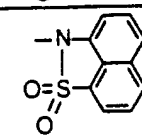
X	A	R_1	R_2	P	B
	-OH	$-CH_3$	H	4	
	-OH	$-CH_2CH_3$	H	4	
	-OH	$-(CH_2)_2CH_3$	H	4	
	-OH	$-CH_3$	$-CH_3$	4	
	-OH	$-CH_2CH_3$	$-CH_3$	4	
	-OH	$-(CH_2)_2CH_3$	$-CH_3$	4	
	-OH	$-CH_2CH_3$	$-CH_2CH_3$	4	
	-OH	$-(CH_2)_2CH_3$	$-CH_2CH_3$	4	
	-OH	$-(CH_2)_2CH_3$	$-(CH_2)_2CH_3$	4	

TABLE II : (continued)

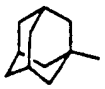
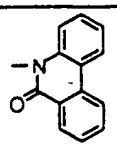
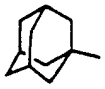
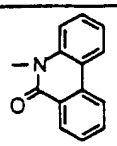
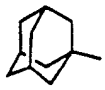
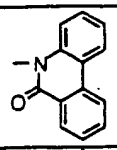
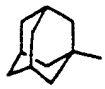
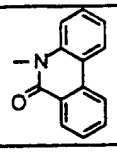
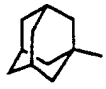
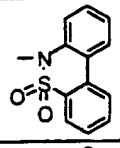
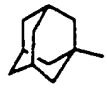
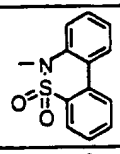
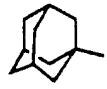
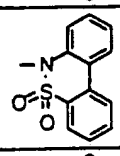
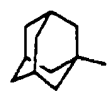
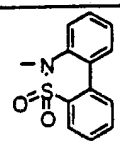
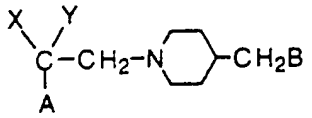
X	A	R_1	R_2	P	B
	-OH	$-CH_3$	H	4	
	-OH	$-CH_2CH_3$	H	4	
	-OH	$-(CH_2)_2CH_3$	H	4	
	-OH	$-CH_3$	$-CH_3$	4	
	-OH	$-CH_3$	H	4	
	-OH	$-CH_2CH_3$	H	4	
	-OH	$-(CH_2)_2CH_3$	H	4	
	-OH	$-CH_3$	$-CH_3$	4	

TABLE III



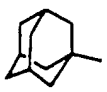
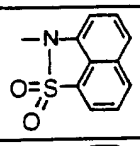
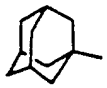
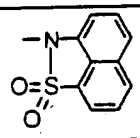
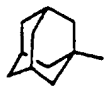
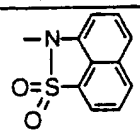
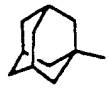
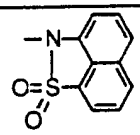
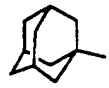
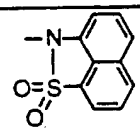
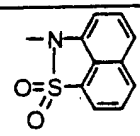
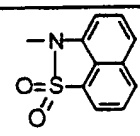
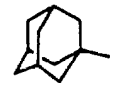
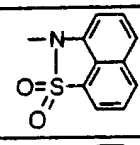
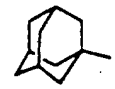
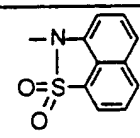
X	Y	A	B
	H	-OH	
	$-CH_3$	-OH	
	$-CH_2CH_3$	-OH	
	$-(CH_2)_2CH_3$	-OH	
	$-(CH_2)_3CH_3$	-OH	
	$-(CH_2)_4CH_3$	-OH	
	$-(CH_2)_5CH_3$	-OH	
	$-CH_2CH=CH_2$	-OH	
	$-(CH_2)_2CH=CH_2$	-OH	

TABLE III : (continued)

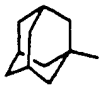
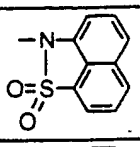
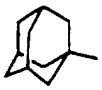
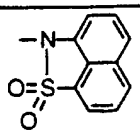
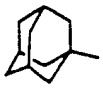
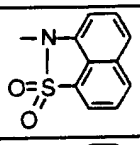
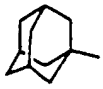
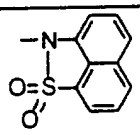
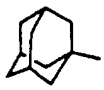
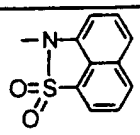
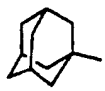
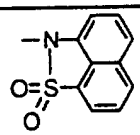
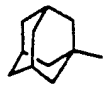
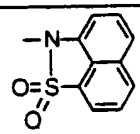
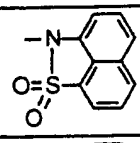
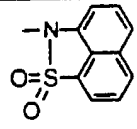
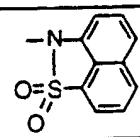
X	Y	A	B
	$-(CH_2)_3CH=CH_2$	-OH	
	$-(CH_2)_4CH=CH_2$	-OH	
		-OH	
		-OH	
		-OH	
	H	$-OCH_3$	
	H	$-OCH_2CH_3$	
	H	$-O(CH_2)_2CH_3$	
	H	$-O(CH_2)_3CH_3$	
	H	$-OCH_2CH=CH_2$	

TABLE III : (continued)

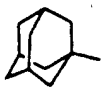
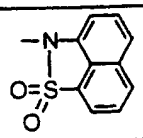
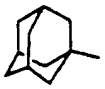
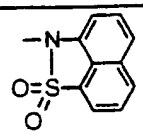
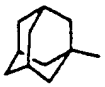
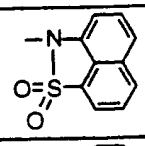
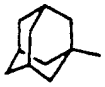
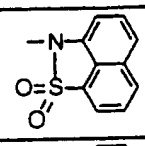
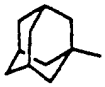
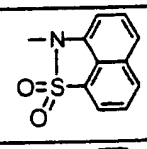
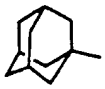
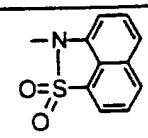
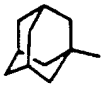
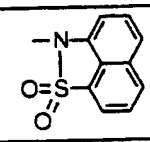
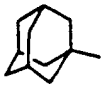
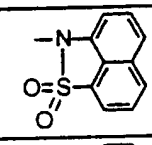
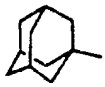
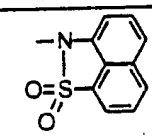
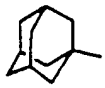
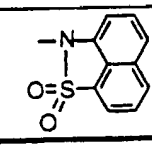
X	Y	A	B
	H	$-O(CH_2)_2CH=CH_2$	
	H	$-O(CH_2)_3CH=CH_2$	
	H	$-O(CH_2)_4CH=CH_2$	
	H	$-O(CH_2)_2OH$	
	H	$-O(CH_2)_3OH$	
	H	$-O(CH_2)_4OH$	
	H	$-NH_2$	
	H	$-NHCH_3$	
	H	$-NHCH_2CH_3$	
	H	$-NH(CH_2)_2CH_3$	

TABLE III : (continued)

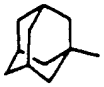
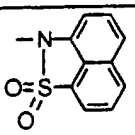
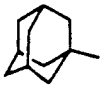
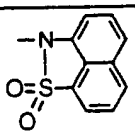
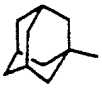
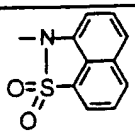
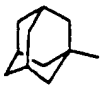
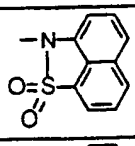
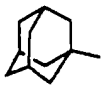
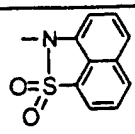
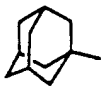
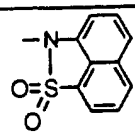
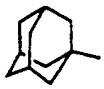
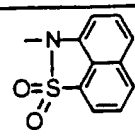
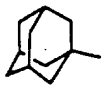
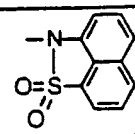
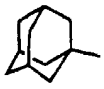
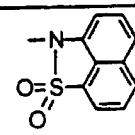
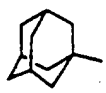
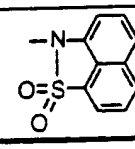
X	Y	A	B
	H	-NHCH$_2$- 	
	H	-NH(CH$_2$)$_2$- 	
	H	-NH(CH$_2$)$_3$- 	
	H	-NHCH$_2$CH=CH$_2$	
	H	-NH(CH$_2$)$_2$CH=CH$_2$	
	H	-NH(CH$_2$)$_3$CH=CH$_2$	
	H	-NH(CH$_2$)$_4$CH=CH$_2$	
	H	-N(CH$_3$)$_2$	
	H	-N(CH$_3$)CH$_2$CH$_3$	
	H	-N(CH$_2$CH$_3$)$_2$	

TABLE III : (continued)

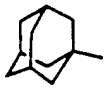
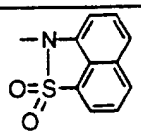
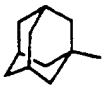
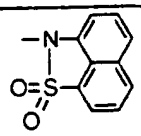
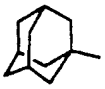
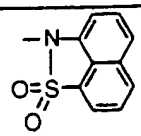
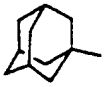
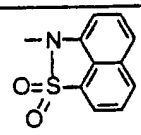
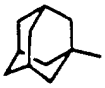
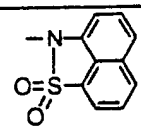
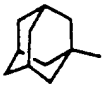
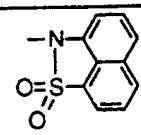
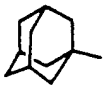
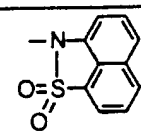
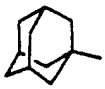
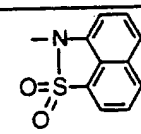
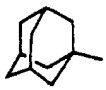
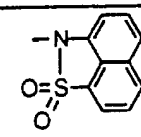
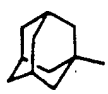
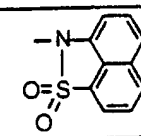
X	Y	A	B
	H	$-N(CH_2CH_2CH_3)_2$	
	H		
	H		
	H	$-NCH_2CH=CH_2$ CH_3	
	H	$-NCH_2CH=CH_2$ CH_2CH_3	
	H	$-N(CH_2)_2CH=CH_2$ $CH_2CH_2CH_3$	
	H		
	H		
	H		
	H		

TABLE III : (continued)

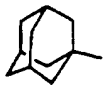
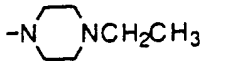
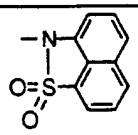
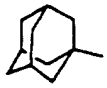
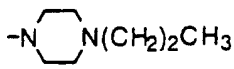
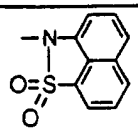
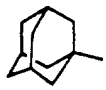
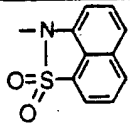
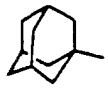
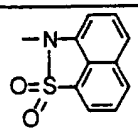
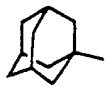
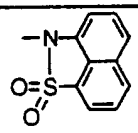
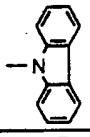
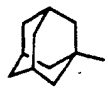
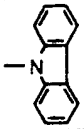
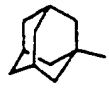
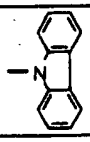
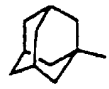
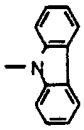
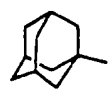
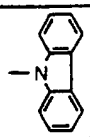
X	Y	A	B
	H		
	H		
	H		
			
			
	H	-OH	
	H	$-OCH_3$	
	H	$-OCH_2CH_3$	
	H	$-O(CH_2)_2CH_3$	
	H	$-OCH_2CH=CH_2$	

TABLE III : (continued)

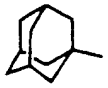
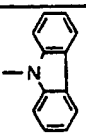
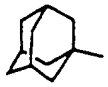
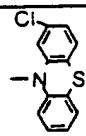
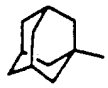
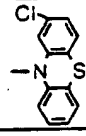
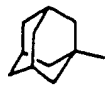
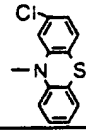
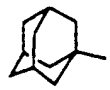
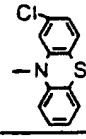
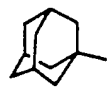
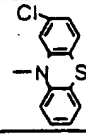
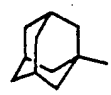
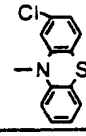
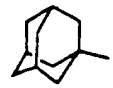
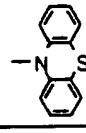
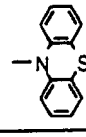
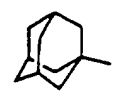
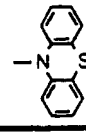
X	Y	A	B
	H	$-O(CH_2)_2OH$	
	H	$-OH$	
	H	$-OCH_3$	
	H	$-OCH_2CH_3$	
	H	$-O(CH_2)_2CH_3$	
	H	$-OCH_2CH{=}CH_2$	
	H	$-O(CH_2)_2OH$	
	H	$-OH$	
	H	$-OCH_3$	
	H	$-OCH_2CH_3$	

TABLE III : (continued)

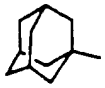
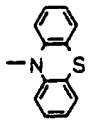
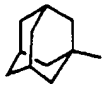
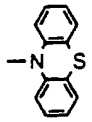
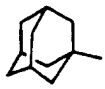
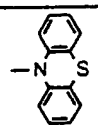
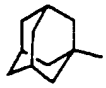
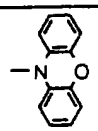
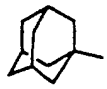
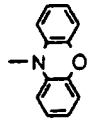
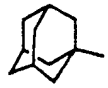
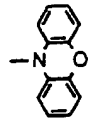
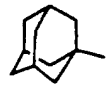
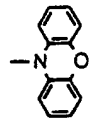
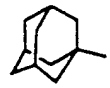
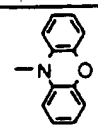
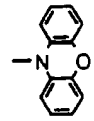
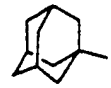
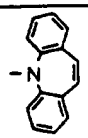
X	Y	A	B
	H	$-O(CH_2)_2CH_3$	
	H	$-OCH_2CH=CH_2$	
	H	$-O(CH_2)_2OH$	
	H	-OH	
	H	$-OCH_3$	
	H	$-OCH_2CH_3$	
	H	$-O(CH_2)_2CH_3$	
	H	$-OCH_2CH=CH_2$	
	H	$-O(CH_2)_2OH$	
	H	-OH	

TABLE III : (continued)

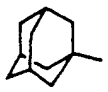
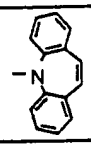
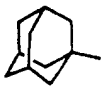
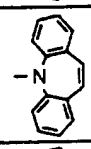
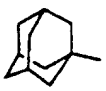
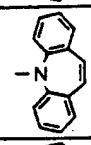
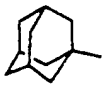
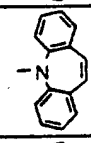
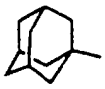
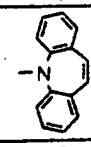
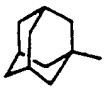
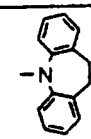
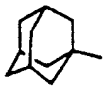
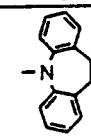
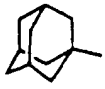
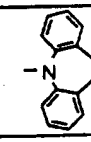
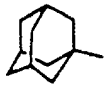
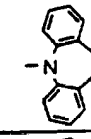
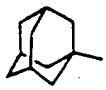
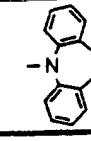
X	Y	A	B
	H	$-OCH_3$	
	H	$-OCH_2CH_3$	
	H	$-O(CH_2)_2CH_3$	
	H	$-OCH_2CH=CH_2$	
	H	$-O(CH_2)_2OH$	
	H	$-OH$	
	H	$-OCH_3$	
	H	$-OCH_2CH_3$	
	H	$-O(CH_2)_2CH_3$	
	H	$-OCH_2CH=CH_2$	

TABLE III : (continued)

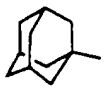
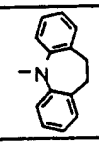
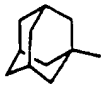
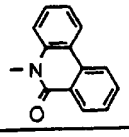
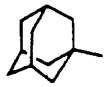
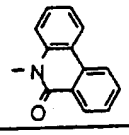
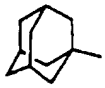
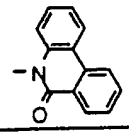
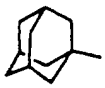
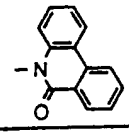
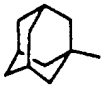
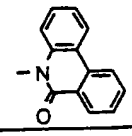
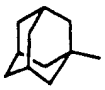
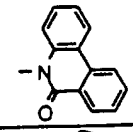
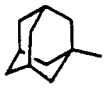
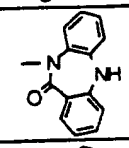
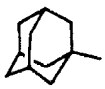
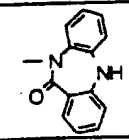
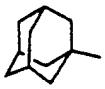
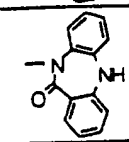
X	Y	A	B
	H	$-O(CH_2)_2OH$	
	H	$-OH$	
	H	$-OCH_3$	
	H	$-OCH_2CH_3$	
	H	$-O(CH_2)_2CH_3$	
	H	$-OCH_2CH=CH_2$	
	H	$-O(CH_2)_2OH$	
	H	$-OH$	
	H	$-OCH_3$	
	H	$-OCH_2CH_3$	

TABLE III : (continued)

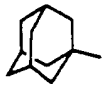
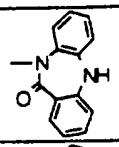
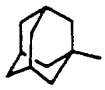
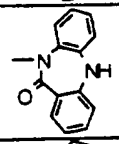
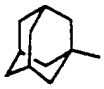
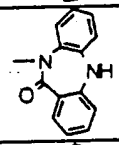
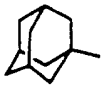
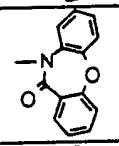
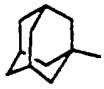
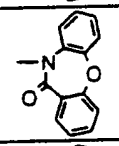
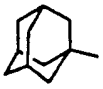
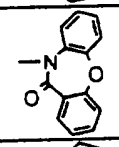
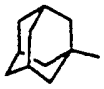
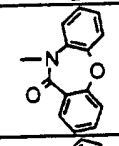
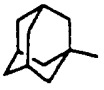
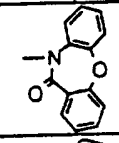
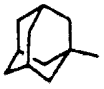
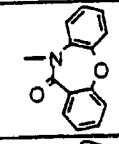
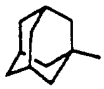
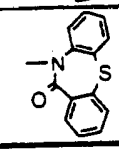
X	Y	A	B
	H	-O(CH$_2$)$_2$CH$_3$	
	H	-OCH$_2$CH=CH$_2$	
	H	-O(CH$_2$)$_2$OH	
	H	-OH	
	H	-OCH$_3$	
	H	-OCH$_2$CH$_3$	
	H	-O(CH$_2$)$_2$CH$_3$	
	H	-OCH$_2$CH=CH$_2$	
	H	-O(CH$_2$)$_2$OH	
	H	-OH	

TABLE III : (continued)

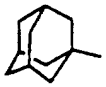
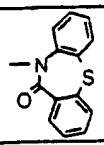
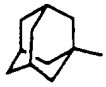
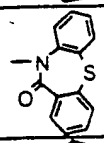
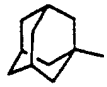
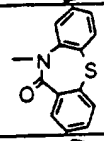
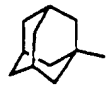
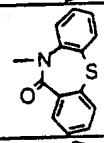
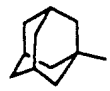
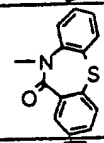
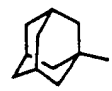
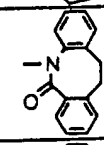
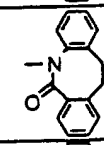
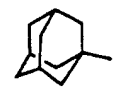
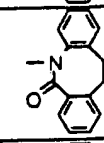
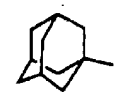
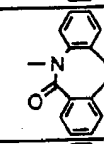
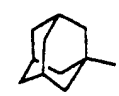
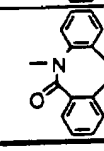
X	Y	A	B
	H	-OCH$_3$	
	H	-OCH$_2$CH$_3$	
	H	-O(CH$_2$)$_2$CH$_3$	
	H	-OCH$_2$CH=CH$_2$	
	H	-O(CH$_2$)$_2$OH	
	H	-OH	
	H	-OCH$_3$	
	H	-OCH$_2$CH$_3$	
	H	-O(CH$_2$)$_2$CH$_3$	
	H	-OCH$_2$CH=CH$_2$	

TABLE III : (continued)

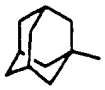
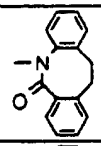
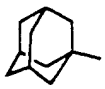
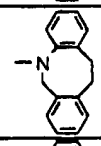
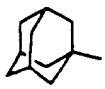
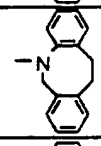
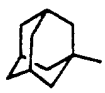
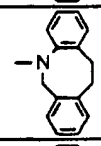
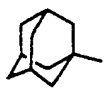
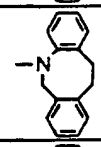
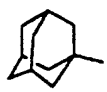
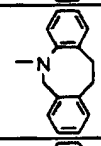
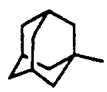
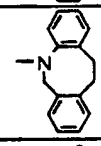
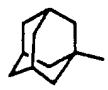
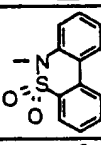
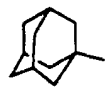
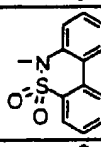
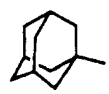
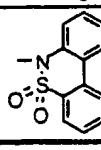
X	Y	A	B
	H	-O(CH$_2$)$_2$OH	
	H	-OH	
	H	-OCH$_3$	
	H	-OCH$_2$CH$_3$	
	H	-O(CH$_2$)$_2$CH$_3$	
	H	-OCH$_2$CH=CH$_2$	
	H	-O(CH$_2$)$_2$OH	
	H	-OH	
	H	-OCH$_3$	
	H	-OCH$_2$CH$_3$	

TABLE III : (continued)

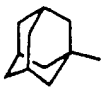
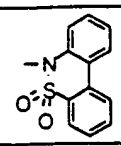
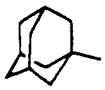
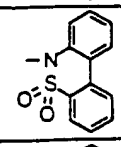
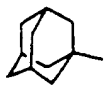
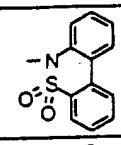
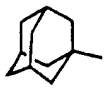
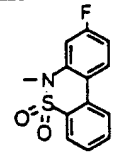
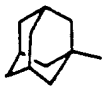
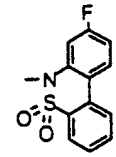
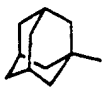
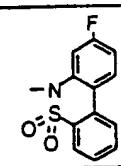
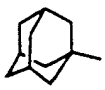
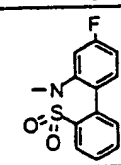
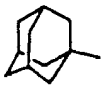
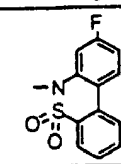
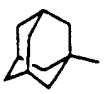
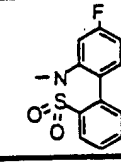
X	Y	A	B
	H	$-O(CH_2)_2CH_3$	
	H	$-OCH_2CH=CH_2$	
	H	$-O(CH_2)_2OH$	
	H	$-OH$	
	H	$-OCH_3$	
	H	$-OCH_2CH_3$	
	H	$-O(CH_2)_2CH_3$	
	H	$-OCH_2CH=CH_2$	
	H	$-O(CH_2)_2OH$	

TABLE III : (continued)

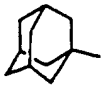
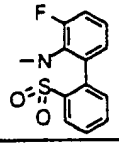
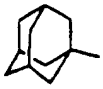
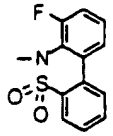
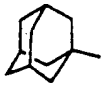
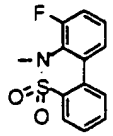
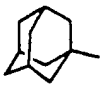
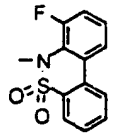
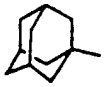
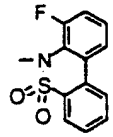
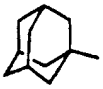
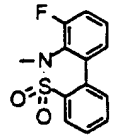
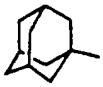
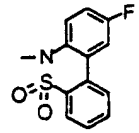
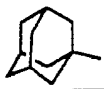
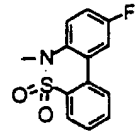
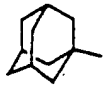
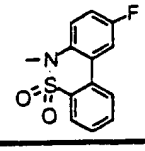
X	Y	A	B
	H	-OH	
	H	$-OCH_3$	
	H	$-OCH_2CH_3$	
	H	$-O(CH_2)_2CH_3$	
	H	$-OCH_2CH=CH_2$	
	H	$-O(CH_2)_2OH$	
	H	-OH	
	H	$-OCH_3$	
	H	$-OCH_2CH_3$	

TABLE III : (continued)

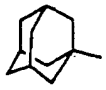
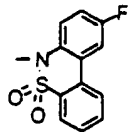
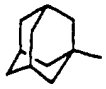
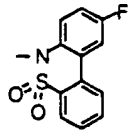
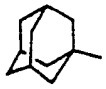
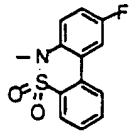
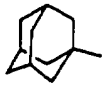
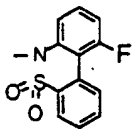
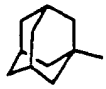
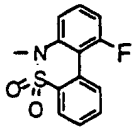
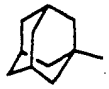
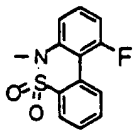
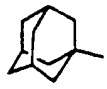
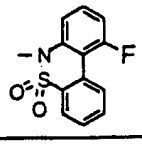
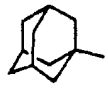
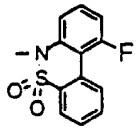
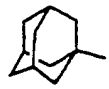
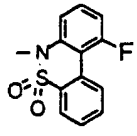
X	Y	A	B
	H	$-O(CH_2)_2CH_3$	
	H	$-OCH_2CH=CH_2$	
	H	$-O(CH_2)_2OH$	
	H	$-OH$	
	H	$-OCH_3$	
	H	$-OCH_2CH_3$	
	H	$-O(CH_2)_2CH_3$	
	H	$-OCH_2CH=CH_2$	
	H	$-O(CH_2)_2OH$	

TABLE III : (continued)

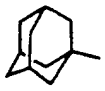
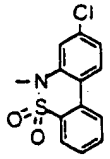
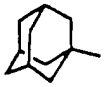
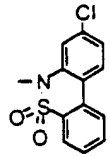
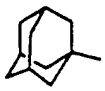
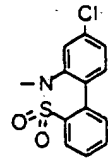
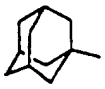
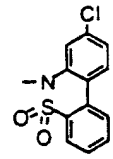
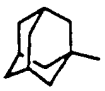
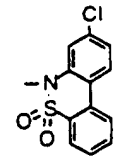
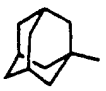
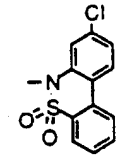
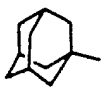
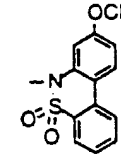
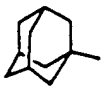
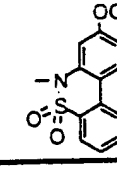
X	Y	A	B
	H	-OH	
	H	$-OCH_3$	
	H	$-OCH_2CH_3$	
	H	$-O(CH_2)_2CH_3$	
	H	$-OCH_2CH=CH_2$	
	H	$-O(CH_2)_2OH$	
	H	-OH	
	H	$-OCH_3$	

TABLE III : (continued)

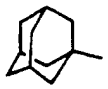
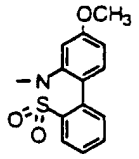
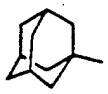
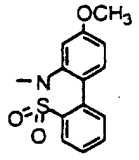
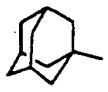
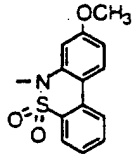
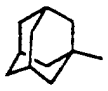
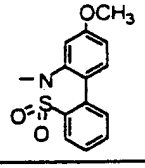
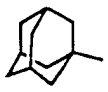
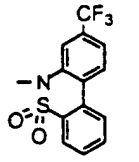
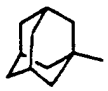
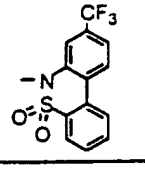
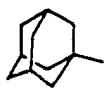
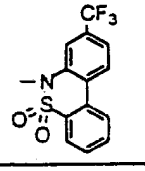
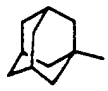
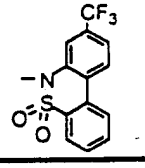
X	Y	A	B
	H	-OCH$_2$CH$_3$	
	H	-O(CH$_2$)$_2$CH$_3$	
	H	-OCH$_2$CH=CH$_2$	
	H	-O(CH$_2$)$_2$OH	
	H	-OH	
	H	-OCH$_3$	
	H	-OCH$_2$CH$_3$	
	H	-O(CH$_2$)$_2$CH$_3$	

TABLE III : (continued)

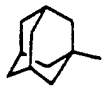
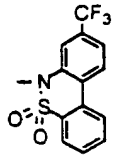
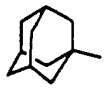
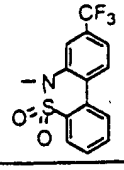
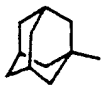
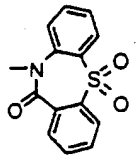
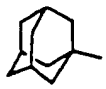
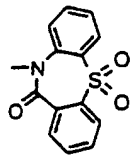
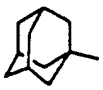
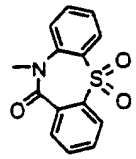
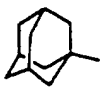
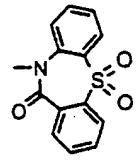
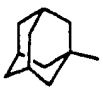
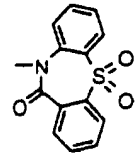
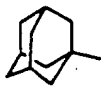
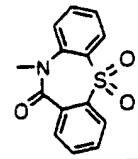
X	Y	A	B
	H	$-OCH_2CH=CH_2$	
	H	$-O(CH_2)_2OH$	
	H	$-OH$	
	H	$-OCH_3$	
	H	$-OCH_2CH_3$	
	H	$-O(CH_2)_2CH_3$	
	H	$-OCH_2CH=CH_2$	
	H	$-O(CH_2)_2OH$	

TABLE III : (continued)

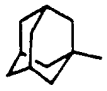
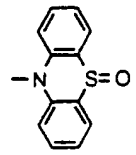
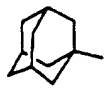
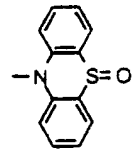
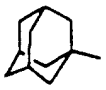
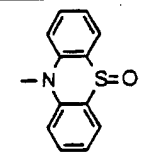
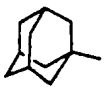
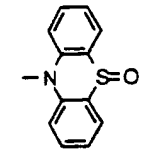
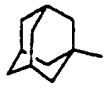
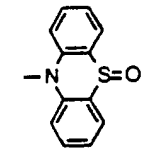
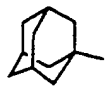
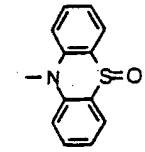
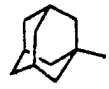
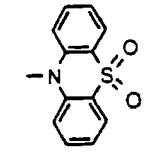
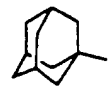
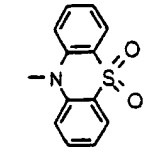
X	Y	A	B
	H	-OH	
	H	$-OCH_3$	
	H	$-OCH_2CH_3$	
	H	$-O(CH_2)_2CH_3$	
	H	$-OCH_2CH=CH_2$	
	H	$-O(CH_2)_2OH$	
	H	-OH	
	H	$-OCH_3$	

TABLE III : (continued)

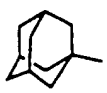
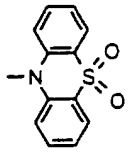
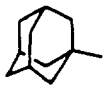
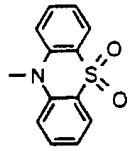
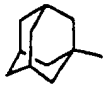
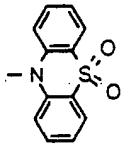
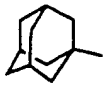
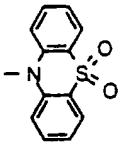
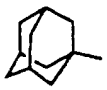
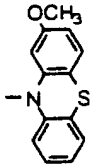
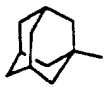
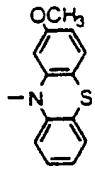
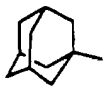
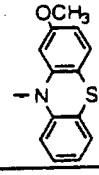
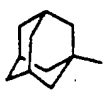
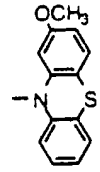
X	Y	A	B
	H	$-OCH_2CH_3$	
	H	$-O(CH_2)_2CH_3$	
	H	$-OCH_2CH=CH_2$	
	H	$-O(CH_2)_2OH$	
	H	$-OH$	
	H	$-OCH_3$	
	H	$-OCH_2CH_3$	
	H	$-O(CH_2)_2CH_3$	

TABLE III : (continued)

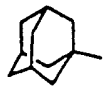
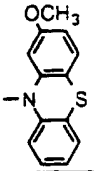
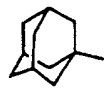
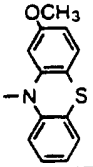
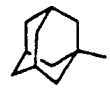
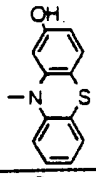
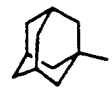
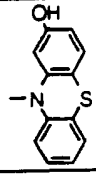
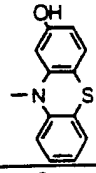
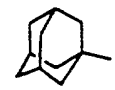
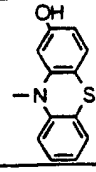
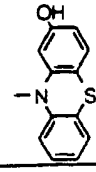
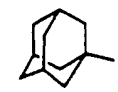
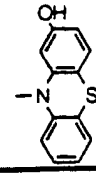
X	Y	A	B
	H	$-OCH_2CH=CH_2$	
	H	$-O(CH_2)_2OH$	
	H	$-OH$	
	H	$-OCH_3$	
	H	$-OCH_2CH_3$	
	H	$-O(CH_2)_2CH_3$	
	H	$-OCH_2CH=CH_2$	
	H	$-O(CH_2)_2OH$	

TABLE III : (continued)

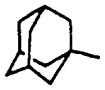
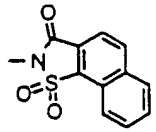
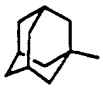
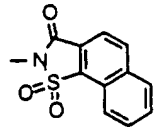
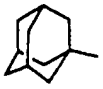
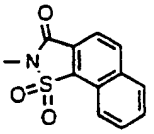
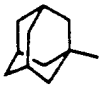
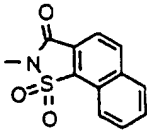
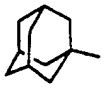
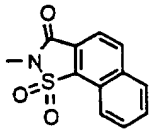
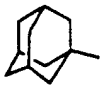
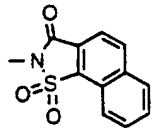
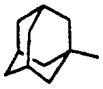
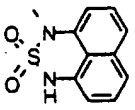
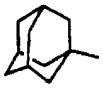
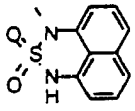
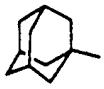
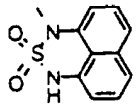
X	Y	A	B
	H	-OH	
	H	$-OCH_3$	
	H	$-OCH_2CH_3$	
	H	$-O(CH_2)_2CH_3$	
	H	$-OCH_2CH=CH_2$	
	H	$-O(CH_2)_2OH$	
	H	-OH	
	H	$-OCH_3$	
	H	$-OCH_2CH_3$	

TABLE III : (continued)

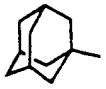
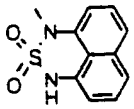
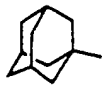
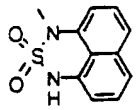
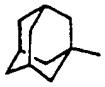
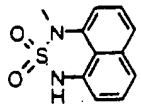
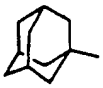
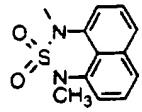
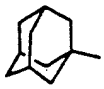
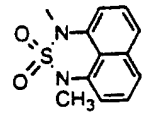
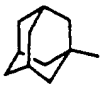
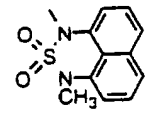
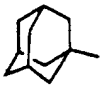
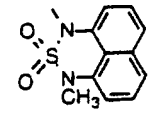
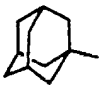
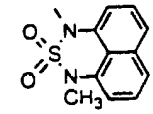
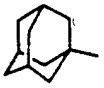
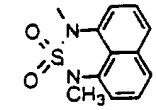
X	Y	A	B
	H	$-O(CH_2)_2CH_3$	
	H	$-OCH_2CH=CH_2$	
	H	$-O(CH_2)_2OH$	
	H	$-OH$	
	H	$-OCH_3$	
	H	$-OCH_2CH_3$	
	H	$-O(CH_2)_2CH_3$	
	H	$-OCH_2CH=CH_2$	
	H	$-O(CH_2)_2OH$	

TABLE III : (continued)

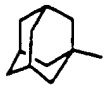
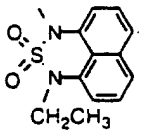
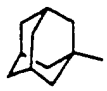
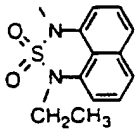
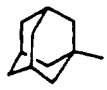
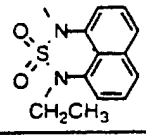
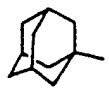
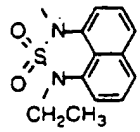
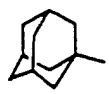
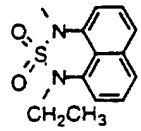
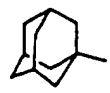
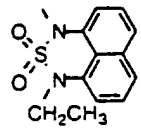
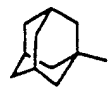
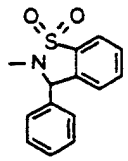
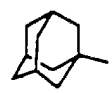
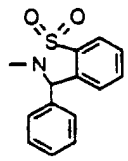
X	Y	A	B
	H	-OH	
	H	-OCH3	
	H	-OCH2CH3	
	H	-O(CH2)2CH3	
	H	-OCH2CH=CH2	
	H	-O(CH2)2OH	
	H	-OH	
	H	-OCH3	

TABLE III : (continued)

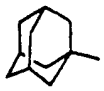
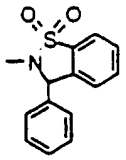
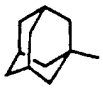
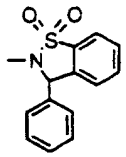
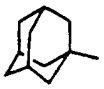
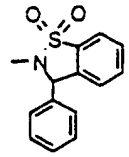
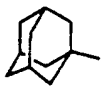
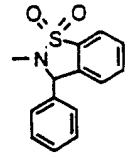
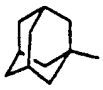
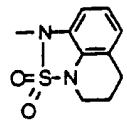
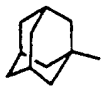
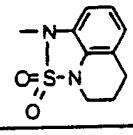
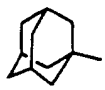
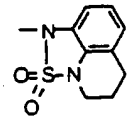
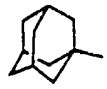
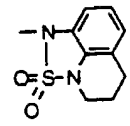
X	Y	A	B
	H	$-OCH_2CH_3$	
	H	$-O(CH_2)_2CH_3$	
	H	$-OCH_2CH=CH_2$	
	H	$-O(CH_2)_2OH$	
	H	$-OH$	
	H	$-OCH_3$	
	H	$-OCH_2CH_3$	
	H	$-O(CH_2)_2CH_3$	

TABLE III : (continued)

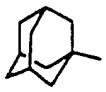
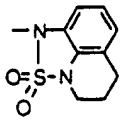
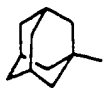
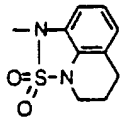
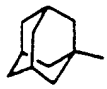
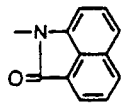
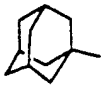
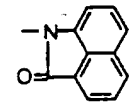
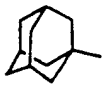
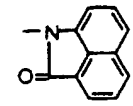
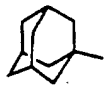
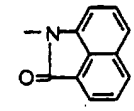
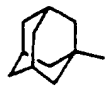
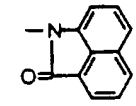
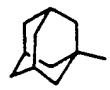
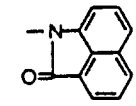
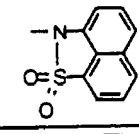
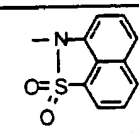
X	Y	A	B
	H	$-OCH_2CH=CH_2$	
	H	$-O(CH_2)_2OH$	
	H	$-OH$	
	H	$-OCH_3$	
	H	$-OCH_2CH_3$	
	H	$-O(CH_2)_2CH_3$	
	H	$-OCH_2CH=CH_2$	
	H	$-O(CH_2)_2OH$	
	H	$-OH$	
	H	$-OCH_3$	

TABLE III : (continued)

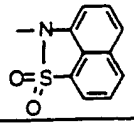
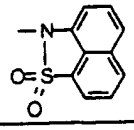
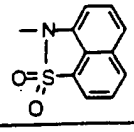
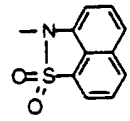
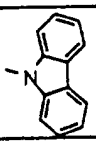
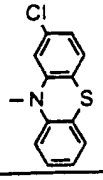
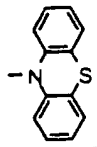
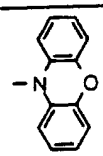
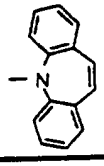
X	Y	A	B
	H	-OCH$_2$CH$_3$	
	H	-O(CH$_2$)$_2$CH$_3$	
	H	-OCH$_2$CH=CH$_2$	
	H	-O(CH$_2$)OH	
	H	-OH	
	H	-OH	
	H	-OH	
	H	-OH	
	H	-OH	

TABLE III : (continued)

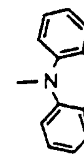
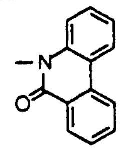
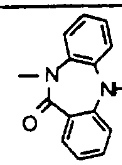
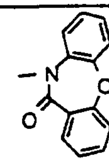
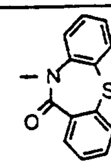
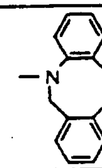
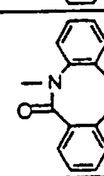
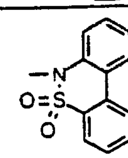
X	Y	A	B
	H	-OH	
	H	-OH	
	H	-OH	
	H	-OH	
	H	-OH	
	H	-OH	
	H	-OH	
	H	-OH	

TABLE III : (continued)

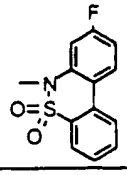
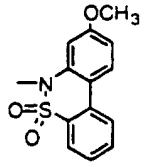
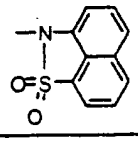
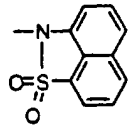
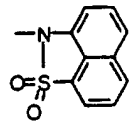
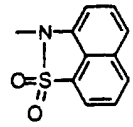
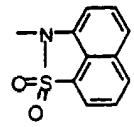
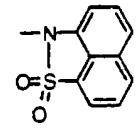
X	Y	A	B
	H	-OH	
	H	-OH	
	$-CH_3$	-OH	
	$-CH_2CH_3$	-OH	
	$-(CH_2)_2CH_3$	-OH	
	$-(CH_2)_5CH_3$	-OH	
	$-CH_2CH=CH_2$	-OH	
	$-(CH_2)_4CH=CH_2$	-OH	

TABLE III : (continued)

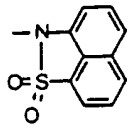
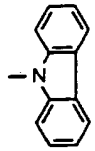
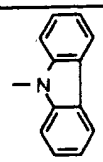
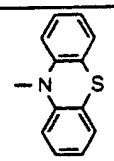
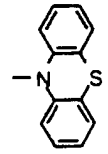
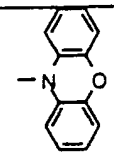
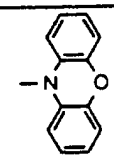
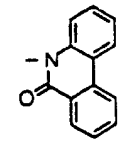
X	Y	A	B
		-OH	
	$-CH_3$	-OH	
	$-CH_2CH_3$	-OH	
	$-CH_3$	-OH	
	$-CH_2CH_3$	-OH	
	$-CH_3$	-OH	
	$-CH_2CH_3$	-OH	
	$-CH_3$	-OH	

TABLE III : (continued)

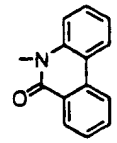
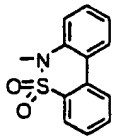
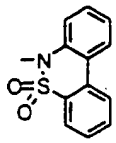
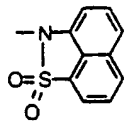
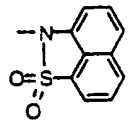
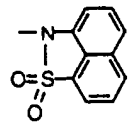
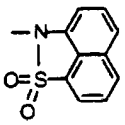
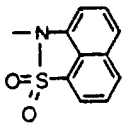
X	Y	A	B
	$-CH_2CH_3$	-OH	
	$-CH_3$	-OH	
	$-CH_2CH_3$	-OH	
	H	-OH	
	H	$-OCH_3$	
	H	$-OCH_2CH_3$	
	H	$-O(CH_2)_2CH_3$	
	H	$-OCH_2CH=CH_2$	

TABLE III : (continued)

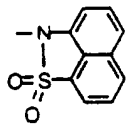
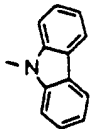
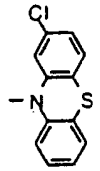
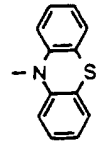
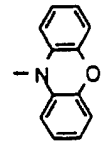
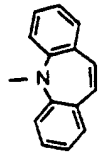
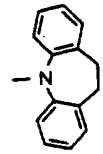
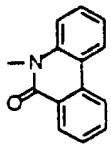
X	Y	A	B
	H	$-O(CH_2)_2OH$	
	H	-OH	
	H	-OH	
	H	-OH	
	H	-OH	
	H	-OH	
	H	-OH	
	H	-OH	

TABLE III : (continued)

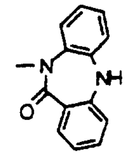
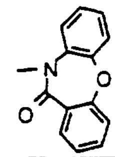
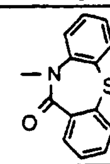
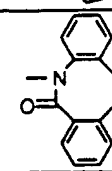
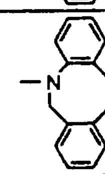
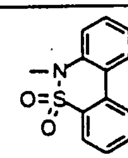
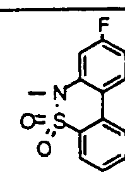
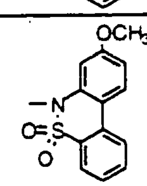
X	Y	A	B
	H	-OH	
	H	-OH	
	H	-OH	
	H	-OH	
	H	-OH	
	H	-OH	
	H	-OH	
	H	-OH	

TABLE III : (continued)

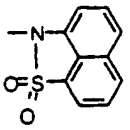
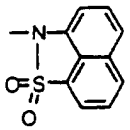
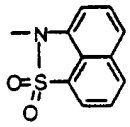
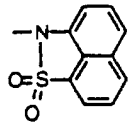
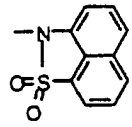
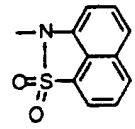
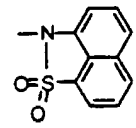
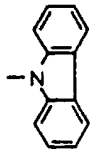
X	Y	A	B
	-CH_3	-OH	
	-CH_2CH_3	-OH	
	-$(CH_2)_2CH_3$	-OH	
	-$(CH_2)_5CH_3$	-OH	
	-$CH_2CH=CH_2$	-OH	
	-$(CH_2)_4CH=CH_2$	-OH	
		-OH	
	-CH_3	-OH	

TABLE III: (continued)

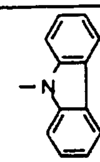
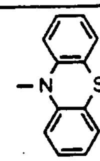
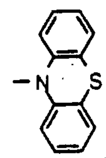
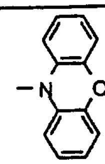
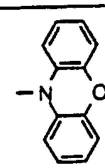
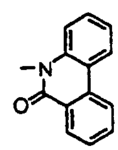
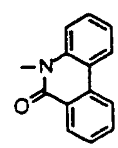
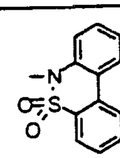
X	Y	A	B
	$-CH_2CH_3$	-OH	
	$-CH_3$	-OH	
	$-CH_2CH_3$	-OH	
	$-CH_3$	-OH	
	$-CH_2CH_3$	-OH	
	$-CH_3$	-OH	
	$-CH_2CH_3$	-OH	
	$-CH_3$	-OH	

TABLE III : (continued)

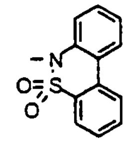
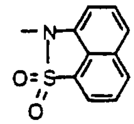
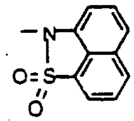
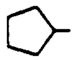
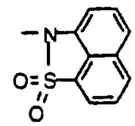
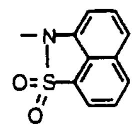
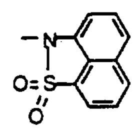
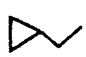
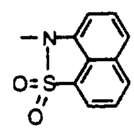
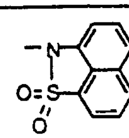
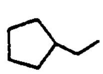
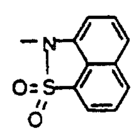
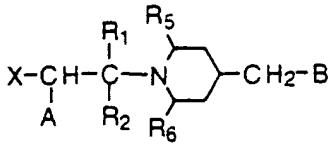
X	Y	A	B
	$-CH_2CH_3$	-OH	
	H	-OH	
	H	-OH	
	H	-OH	
	H	-OH	
	H	-OH	
	H	-OH	
	H	-OH	
	H	-OH	

TABLE IV :



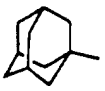
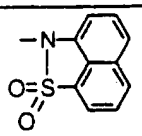
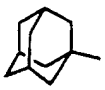
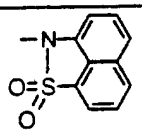
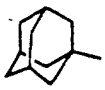
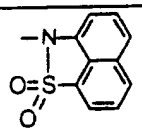
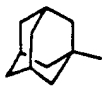
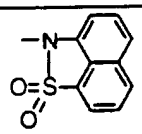
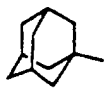
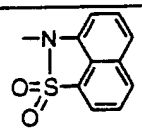
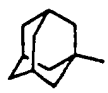
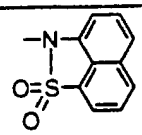
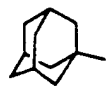
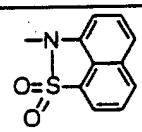
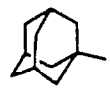
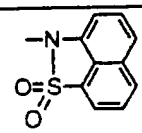
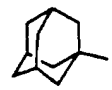
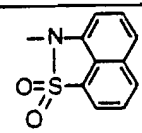
X	A	R_1	R_2	R_5	R6	B
	-OH	$-CH_3$	H	H	H	
	-OH	$-CH_2CH_3$	H	H	H	
	-OH	$-(CH_2)_2CH_3$	H	H	H	
	-OH	$-CH_3$	$-CH_3$	H	H	
	-OH	$-CH_2CH_3$	$-CH_3$	H	H	
	-OH	$-(CH_2)_2CH_3$	$-CH_3$	H	H	
	-OH	$-CH_2CH_3$	$-CH_2CH_3$	H	H	
	-OH	$-(CH_2)_2CH_3$	$-CH_2CH_3$	H	H	
	-OH	$-(CH_2)_2CH_3$	$-(CH_2)_2CH_3$	H	H	

TABLE IV : (continued)

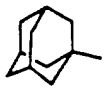
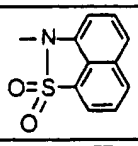
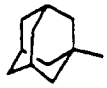
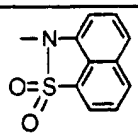
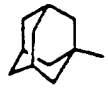
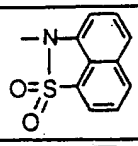
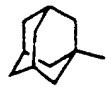
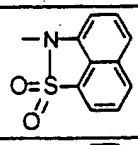
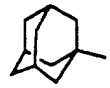
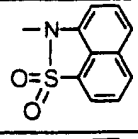
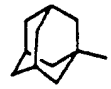
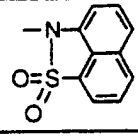
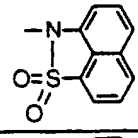
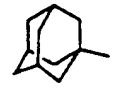
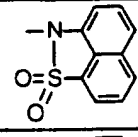
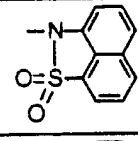
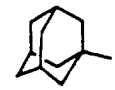
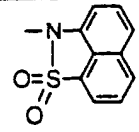
X	A	R_1	R_2	R_5	R6	B
	-OH	H	H	$-CH_3$	H	
	-OH	H	H	$-CH_3$	$-CH_3$	
	-OH	$-CH_3$	H	$-CH_3$	H	
	-OH	$-CH_3$	H	$-CH_3$	$-CH_3$	
	-OH	$-CH_2CH_3$	H	$-CH_3$	H	
	-OH	$-CH_2CH_3$	H	$-CH_3$	$-CH_3$	
	-OH	$-(CH_2)_2CH_3$	H	$-CH_3$	H	
	-OH	$-(CH_2)_2CH_3$	H	$-CH_3$	$-CH_3$	
	-OH	$-CH_3$	$-CH_3$	$-CH_3$	H	
	-OH	$-CH_3$	$-CH_3$	$-CH_3$	$-CH_3$	

TABLE IV : (continued)

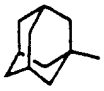
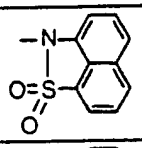
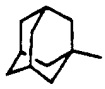
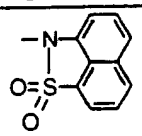
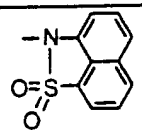
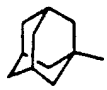
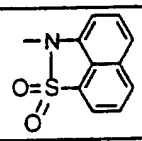
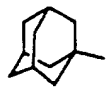
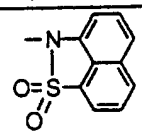
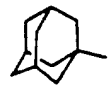
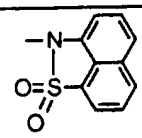
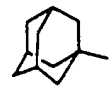
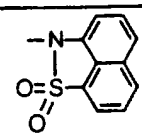
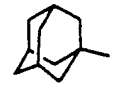
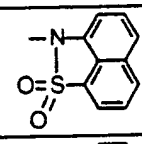
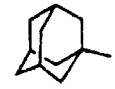
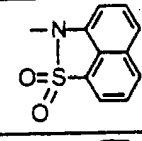
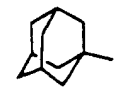
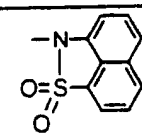
X	A	R_1	R_2	R_5	R6	B
	-OH	$-CH_2CH_3$	$-CH_3$	$-CH_3$	H	
	-OH	$-CH_2CH_3$	$-CH_3$	$-CH_3$	$-CH_3$	
	-OH	$-(CH_2)_2CH_3$	$-CH_3$	$-CH_3$	H	
	-OH	$-(CH_2)_2CH_3$	$-CH_3$	$-CH_3$	$-CH_3$	
	-OH	$-CH_2CH_3$	$-CH_2CH_3$	$-CH_3$	H	
	-OH	$-CH_2CH_3$	$-CH_2CH_3$	$-CH_3$	$-CH_3$	
	-OH	$-(CH_2)_2CH_3$	$-CH_2CH_3$	$-CH_3$	H	
	-OH	$-(CH_2)_2CH_3$	$-CH_2CH_3$	$-CH_3$	$-CH_3$	
	-OH	$-(CH_2)_2CH_3$	$-(CH_2)_2CH_3$	$-CH_3$	H	
	-OH	$-(CH_2)_2CH_3$	$-(CH_2)_2CH_3$	$-CH_3$	$-CH_3$	

TABLE IV : (continued)

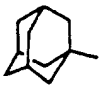
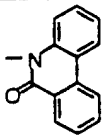
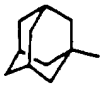
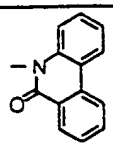
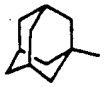
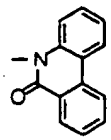
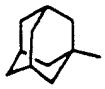
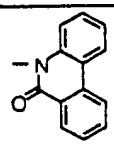
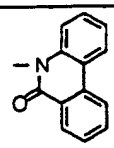
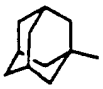
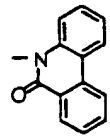
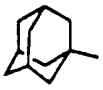
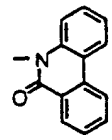
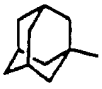
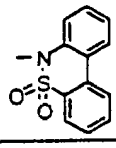
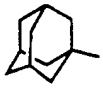
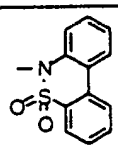
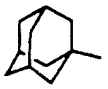
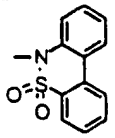
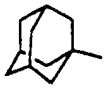
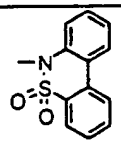
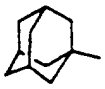
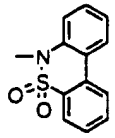
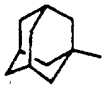
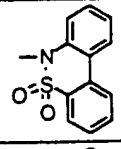
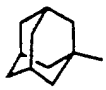
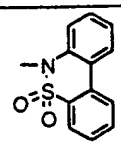
X	A	R_1	R_2	R_5	R6	B
	-OH	$-CH_3$	H	H	H	
	-OH	$-CH_2CH_3$	H	H	H	
	-OH	$-(CH_2)_2CH_3$	H	H	H	
	-OH	$-CH_3$	$-CH_3$	H	H	
	-OH	H	H	$-CH_3$	H	
	-OH	H	H	$-CH_3$	$-CH_3$	
	-OH	$-CH_3$	$-CH_3$	$-CH_3$	$-CH_3$	
	-OH	$-CH_3$	H	H	H	
	-OH	$-CH_2CH_3$	H	H	H	

TABLE IV : (continued)

X	A	R_1	R_2	R_5	R6	B
	-OH	$-(CH_2)_2CH_3$	H	H	H	
	-OH	$-CH_3$	$-CH_3$	H	H	
	-OH	H	H	$-CH_3$	H	
	-OH	H	H	$-CH_3$	$-CH_3$	
	-OH	$-CH_3$	$-CH_3$	$-CH_3$	$-CH_3$	

Specifically preferred compounds are :

1-(1-Adamantyl)-2-[N-methyl-N-[4-(2H-naphth[1,8-*cd*]isothiazol-2-yl)butyl]amino]ethanol S,S-dioxide;

2-[[1-[2-(1-Adamantyl)-2-oxoethyl]-4-piperidinyl]methyl]-2H-naphth[1,8-*cd*]isothiazole 1,1-dioxide;

2-[[1-[2-(1-Adamantyl)-2-oximinoethyl]-4-piperidinyl]methyl]-2H-naphth[1,8-*cd*]isothiazole 1,1-dioxide;

1-(1-Adamantyl)-2-[4-(2H-naphth[1,8-*cd*]isothiazol-2-ylmethyl)piperidin-1-yl]ethanol S,S-dioxide;

1-(1-Adamantyl)-2-[4-(9-carbazolyl)methylpiperidin-1-yl]ethanol;

1-(1-Adamantyl)-2-[N-methyl-N-[4-(2H-naphth[1,8-*cd*]isothiazol-2-yl)butyl]amino]ethylamine S,S-dioxide;

1-(1-Adamantyl)-N-methyl-2-[N-methyl-N-[4-(2H-naphth[1,8-*cd*]isothiazol-2-yl)butyl]amino]ethylamine S,S-dioxide;

2-(1-Adamantyl)-N-methyl-N-[4-(2H-naphth[1,8-*cd*]isothiazol-2-yl)butyl]-2-pyrrolidin-1-ylethylamine S,S-dioxide;

2-[4-[N-[2-(1-Adamantyl)-2-methoxyethyl]-N-methylamino]butyl]-2H-naphth[1,8-*cd*]isothiazole 1,1-dioxide;

1-(1-Adamantyl)-2-[N-methyl-N-[4-[5H-phenanthridin-6-oxo-5-yl]butyl]amino]ethanol;

1-(1-Adamantyl)-2-[N-methyl-N-[4-(6H-dibenzo[*ce*][1,2]thiazin-6-yl)butyl]amino]ethanol S,S-dioxide;

1-(1-Adamantyl)-2-[4-(2H-naphth[1,8-*cd*]isothiazol-2-ylmethyl)piperidin-1-yl]ethylamine S,S-dioxide;

1-(1-Adamantyl)-N-methyl-2-[4-(2*H*-naphth[1,8-*cd*]isothiazol-2-ylmethyl)piperidin-1-yl]ethylamine S,S-dioxide;

2-[1-[2-(1-Adamantyl)-2-morpholin-4-ylethyl]piperidin-4-ylmethyl]-2H-naphth[1,8-*cd*]isothiazole 1,1-dioxide;

2-[1-[2-(1-Adamantyl)-2-pyrrolidin-1-ylethyl]piperidin-4-ylmethyl]-2H-naphth[1,8-*cd*]isothiazole 1,1-dioxide;

2-[1-[2-(1-Adamantyl)-2-(4-methyl)piperazin-1-ylethyl]piperidin-4-ylmethyl]-2H-naphth[1,8-*cd*]isothiazole 1,1-dioxide;

1-(1-Adamantyl)-N,N-diethyl-2-[4-(2H-naphth[1,8-*cd*]isothiazol-2-ylmethyl)piperidin-1-yl]ethylamine S,S-dioxide;

1-(1-Adamantyl)-N-allyl-N-methyl-2-[4-(2H-naphth[1,8-*cd*]isothiazol-2-ylmethyl)piperidin-1-yl]ethylamine S,S-dioxide;

2-[1-[2-(1-Adamantyl)-2-methoxyethyl]piperidin-4-ylmethyl]-2H-naphth[1,8-*cd*]isothiazole 1,1-dioxide;

2-[1-[2-(1-Adamantyl)-2-ethoxyethyl]piperidin-4-ylmethyl]-2H-naphth[1,8-*cd*]isothiazole 1,1-dioxide;

1-(1-Adamantyl)-1-methyl-2-[4-(2H-naphth[1,8-*cd*]isothiazol-2-ylmethyl)piperidin-1-yl]ethanol S,S-dioxide;

1-Cyclohexyl-2-[4-(2H-naphth[1,8-*cd*]isothiazol-2-ylmethyl)piperidin-1-yl]ethanol S,S-dioxide;

1-(1-Adamantyl)-2-[4-(2-chlorophenothiazin-10-ylmethyl)piperidin-1-yl]-ethanol;

1-(1-Adamantyl)-2-[4-(phenothiazin-10-ylmethyl)piperidin-1-yl]ethanol;

1-(1-Adamantyl)-2-[4-(phenoxazin-10-ylmethyl)piperidin-1-yl]ethanol;

1-(1-Adamantyl)-2-[4-(5H-dibenz[b,f]azepin-5-ylmethyl)piperidin-1-yl]ethanol;

1-(1-Adamantyl)-2-[4-(10,11-dihydro-5H-dibenz[b,f]azepin-5-ylmethyl)-piperidin-1-yl]ethanol;

1-(1-Adamantyl)-2-[4-(5H-phenanthridin-6-oxo-5-ylmethyl)piperidin-1-yl]ethanol;

1-(1-Adamantyl)-2-[4-(10,11-dihydrodibenz[b,f][1,4]oxazepin-11-oxo-10-ylmethyl)piperidin-1-yl]ethanol;

1-(1-Adamantyl)-2-[4-(10,11-dihydrodibenzo[b,e][1,4]diazepin-11-oxo-10-ylmethyl)piperidin-1-yl]ethanol;

1-(1-Adamantyl)-2-[4-(10,11-dihydrodibenzo[b,f][1,4]thiazepin-11-oxo-10-ylmethyl)piperidin-1-yl]ethanol;

1-(1-Adamantyl)-2-[4-(5,6,11,12-tetrahydrodibenz[b,f]azocin-6-oxo-5-ylmethyl)piperidin-1-yl]ethanol;

1-(1-Adamantyl)-2-[4-(5,6,11,12-tetrahydrodibenz[b,f]azocin-5-ylmethyl)piperidin-1-yl]ethanol;

1-(1-Adamantyl)-2-[4-(6H-dibenzo[c,e][1,2]thiazin-6-ylmethyl)piperidin-1-yl]ethanol S,S-dioxide;

6-[1-[2-(1-Adamantyl)-2-methoxyethyl]piperidin-4-ylmethyl]-6H-dibenzo[c,e][1,2]thiazine 5,5-dioxide;

1-(1-Adamantyl)-2-[4-(7-fluoro-6H-dibenzo[c,e][1,2]thiazin-6-ylmethyl)-piperidin-1-yl]ethanol S,S-dioxide;

1-(1-Adamantyl)-2-[4-(8-fluoro-6H-dibenzo[c,e][1,2]thiazin-6-ylmethyl)-piperidin-1-yl]ethanol S,S-dioxide;

1-(1-Adamantyl)-2-[4-(9-fluoro-6H-dibenzo[c,e][1,2]thiazin-6-ylmethyl)-piperidin-1-yl]ethanol S,S-dioxide;

1-(1-Adamantyl)-2-[N-methyl-N-[4-(10,11-dihydrodibenz[b,f][1,4]-oxazepin-11-oxo-10-yl)butyl]amino]ethanol;

10-[4-[N-[2-(1-Adamantyl)-2-methoxyethyl]-N-methylamino]butyl]-10,11-dihydrodibenz[b,f][1,4]oxazepin-11-one;

1-(1-Adamantyl)-2-[N-methyl-N-[4-(10,11-dihydrodibenzo[b,f][1,4]-thiazepin-11-oxo-10-yl)butyl]amino]ethanol;

10-[4-[N-[2-(1-Adamantyl)-2-methoxyethyl]-N-methylamino]butyl]-10,11-dihydrodibenzo[b,f][1,4]thiazepin-11-one;

5-[4-[N-[2-(1-Adamantyl)-2-methoxyethyl]-N-methylamino]butyl]-5H-phenanthridin-6-one;

1-(1-Adamantyl)-2-[4-(8-chloro-6H-dibenzo[c,e][1,2]thiazin-6-ylmethyl)-piperidin-1-yl]ethanol S,S-dioxide;

1-(1-Adamantyl)-2-[4-(8-methoxy-6H-dibenzo[c,e][1,2]thiazin-6-ylmethyl)-piperidin-1-yl]ethanol S,S-dioxide;

Wherein said compounds are both the racemic mixture or the individual optical isomers.

Compounds of the present invention can exist as optical isomers and both the racemic mixture of the isomers as well as the individual optical isomers are within the scope of this invention. The racemic mixtures can be separated into their individual isomers by techniques well known to those skilled in the art.

The present invention also relates to the pharmaceutically acceptable acid addition salts of compounds of the formula (I) or pharmaceutically acceptable carriers or diluents.

The present invention relates to a method of treating or preventing a condition in a mammal, including a human, the treatment or prevention of which is affected or facilitated by the neuromodulatory effect of sigma 2 ligands.

The present invention relates to a method of treating or preventing a condition selected from the group consisting of anxiety, depression or dysthymic disorders, psychosis, pain, dyskinesia, ischaemia induced brain disorders, convulsions, stroke, epilepsy, dementia, parkinsonism, neuropathological disorders and memory impairment, hypertension, arrhythmia and angina.

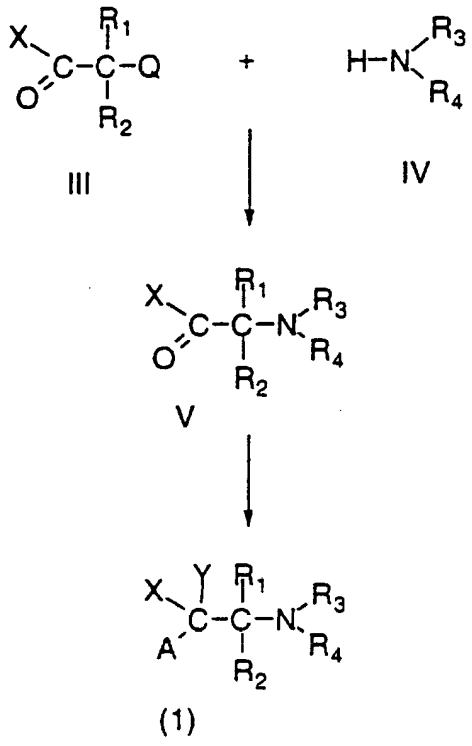
The present invention relates to pharmaceutical compositions which provide from about 0.01 to 100 mg of the active ingredient per unit dose. The compositions may be administered by any suitable route. For example orally in the form of tablets or capsules, etc..., parenterally in the form of solutions for injection, topically in the form of onguents or lotions, ocularly in the form of eye-lotion. For preparing such compositions, methods well known in the art may be used; the nature of the pharmaceutical composition employed will depend on the desired route of administration.The total daily dose usually ranges from about 0.05 - 500 mg.

The compounds of Formula (I) may be prepared by general route of synthesis as disclosed in the following methods.

Method A :

Scheme A1 illustrates the preparation of compounds of the formula (I). A compound of the formula III where Q includes halides such as Cl, Br, I or tosylate, mesylate, is reacted with the nucleophilic amino derivative IV to yield the corresponding compound V. The reaction is typically carried out in the presence of a base such as triethylamine or potassium carbonate in a polar solvent like dimethylformamide, acetonitrile.

Scheme A1



The amino-keto derivative may be reduced to give the hydroxy derivative of formula (I) of the invention where A = OH and Y = H. The reduction is generally accomplished by using sodium borohydride in ethanol, methanol or tetrahydrofuran at room temperature.

The amino-keto derivative may be converted into aminoalcohols by reaction with organometallic reagents such as Y-MgBr or Y-Li to give compounds of the invention where A = OH and Y as defined in the description of formula (I).

Alkoxy molecules may be prepared by standard methods familiar to those skilled in the art by converting the free hydroxy derivative; O-alkyl derivatives may be carried out by the solvolysis of a sulfonyl ester intermediate [Advanced Organic Chemistry, J. March, John Wiley & sons, New York, 1985, 264-317]; the solvolysis of a chiral sulfonyl ester derivative in the above ethanolamine series of general structure (I) where A = OH, affords a chiral ether.

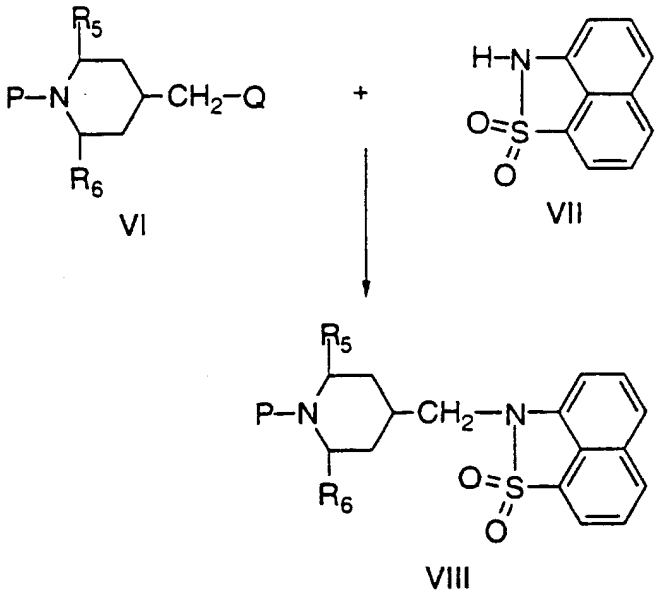
The oxime of the keto derivative V is prepared according to oximation method as described in Organic Functional Group Preparation Vol. III [S.R. Sandler and W. Karo, Academic Press, London, 1989, 430-481].

The keto derivative V may be the precursor of the amino derivatives of formula (I) where Y = H and A = -N (R_{10}, R_{11}) via reductive amination [Comprehensive organic transformations, R.C. Larock, VCH Publishers, New York, 1989, 421-425] or by the Leuckart reaction [M.L. Moore, Org. Reactions, 1949, 5, 7, 301]. Such amino derivatives may be prepared from the hydroxy derivative of formula (I) where A = OH by the Mitsunobu reaction [O. Mitsunobu, Synthesis, 1981, 1-28]. The conversion by standard methods of the hydroxy group to a leaving group like Q (e.g. halide, mesylate) and subsequent substitution by an amino group to give an amino derivative is also a general method of synthesis.

The reaction of substitution may be carried out with sodium azide to give an azide. The azido derivative may be reduced to give primary amine [Comprehensive organic transformations, R.C. Larock, VCH Publishers, New York, 1989, 409-410].

The oximino derivative prepared as described above can also be reduced to give the free amino derivative by standard reduction process like catalytic hydrogenation over platinum oxide or palladium on carbon or chemical reduction with lithium aluminum hydride.

Scheme A 2



The synthesis of the starting amino compound IV presented in scheme A1 is depicted in the scheme A2.

The target amino derivative VIII has been chosen in the piperidino series, however, acyclic amino derivatives may be obtained according to the same process. The P substituent in the compounds of formula VI and VIII represents a protective group like those described in Protective Groups in Organic Synthesis [T.W. Greene and P.G.M. Wuts, John Wiley & Sons, New York, 1991]. This protecting group is easily removed to give the piperidino analogue of formula IV. The N-alkylation reaction is preferably conducted in dimethylformamide in the presence of sodium hydride as base and at a temperature above 50 °C. The reaction can also be conducted under phase transfer process using toluene as solvent, sodium or potassium hydroxide as base, in the presence of catalytic amount of tetrabutylammonium hydrogen sulfate or other suitable salt. This route of synthesis can be extended to other heteroaryl rings of formula B as depicted in the description of invention.

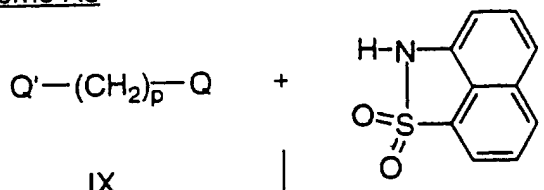
The heteroaryl ring of formula B may be purchased from commercial sources or they may be prepared via known methods. The synthesis of ring substituted

6H-dibenzo[c,e][1,2]thiazine S,S-dioxide may be accomplished by employing the method described by F. Ullmann and C. Grob in Chem. Ber. 1910, 43,2694 for unsubstituted sultam.

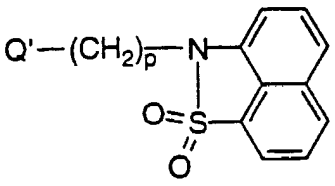
Another route of synthesis of the starting amino compound IV is illustrated in scheme A3. The N-alkylation of the naphthosultam VII may be conducted acccording to the process described by J.L. Malleron, M.T. Comte, C. Gueremy, J.F. Peyronel, A. Truchon, J.C. Blanchard, A. Doble, O. Piot, J.L. Zundel, C. Huon, B. Martin, P. Moutin, A. Viroulaud, D. Allam and J. Betschart [J. Med. Chem. 1991, 34, 2477-2483]. This route of synthesis can be extended to other heteroaryl rings of formula B as depicted in the description of invention.

Q' is generally another electrophilic group which could be interconverted to Q and reacted with the N-protected amino derivative XI to give XII. The removal of the protective group from the amino precursors VIII and XII is accomplished by standard process and gives the resulting amine IV.

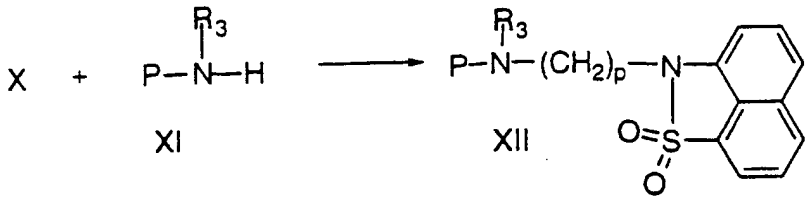
Scheme A3



IX VII



X

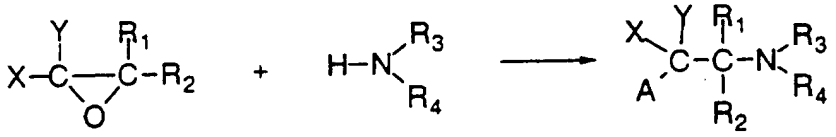


XI XII

Method B

Another route for the preparation of the compounds of formula (I) where A = OH is outlined in Scheme B1. The aminolysis of epoxy derivatives is a classical reaction which is generally conducted by heating the reactives in a solvent like ethanol [N.S. Isaacs and R.E.Parker, J. , 1960, 3497-3504]; aminolysis reaction may be performed by using metal salts as catalysts [M. Chini, P.Crotti and F.Macchia, Tetrahedron Letters, 1990, 31,32,4661-4664].
The epoxy derivative XIII may be obtained according to different usual methods : oxidation of an alkenyl derivative, dehydrohalogenation of a halohydrin, synthesis starting from a carboxaldehyde.

Scheme B1



XIII IV (1)

When the starting epoxy derivative XIII is used in an optically active form, the final amino alcohol (I) is obtained in an optically active form.

The relevant starting material in the above-mentioned processes may be in racemic form or in the desired optically active form to give racemic or optically active compounds.

The desired optically active enantiomer may also be obtained by resolution according to conventional techniques.

The compounds of the formula (I) which are basic in nature can form a wide variety of different pharmaceutically acceptable salts with various inorganic and organic acids. These salts are readily prepared by treating the base compound with a substancially equivalent amount of the chosen mineral or organic acid in a suitable organic solvent such as methanol, ethanol or isopropanol.

Best Mode for Carrying Out the Invention

In the followinntion is further illustrated by examples which, however, may not be consg, the invetrued as limiting :

(i) column chromatography was carried out on Merck Kieselgel (Art 9335); thin layer chromatography (TLC) was carried out on Merck 0.2 mm silica gel 60F_{254} plates (Art 1.05735);

(ii) in general, the course of reactions was followed by TLC and reaction times are given for illustration only;

(iii) melting points (m.p.) are uncorrected and (dec) indicates decomposition;

(iv) solvent ratios are given in volume:volume terms;

(v) ^{1}H-NMR: 200 MHz, δ in ppm.

EXAMPLE 1

(R,S)-1-(1-Adamantyl)-2-[N-methyl-N-[4-(2H-naphth[1,8-*cd*]isothiazol-2-yl)butyl]amino]ethanol S,S-dioxide, fumarate.

a) 2-(4-Iodobutyl)-2H-naphth[1,8-cd]isothiazole 1,1-dioxide.

2-(4-Chlorobutyl)-2H-naphth[1,8-cd]isothiazole 1,1-dioxide (62.9 g, 212.8 mmol) [prepared as described by J.L. Malleron, M.T. Comte, C. Gueremy, J.F. Peyronel, A. Truchon, J.C. Blanchard, A. Doble, O. Piot, J.L. Zundel, C. Huon, B. Martin, P. Moutin, A. Viroulaud, D. Allam and J. Betschart, J. Med. Chem. 1991, 34, 2477-2483] was added to methylethylketone (400 ml) containing sodium iodide (64.5 g, 430 mmol). The heterogeneous mixture was heated under reflux for 4 hours. After cooling, the solution was filtered and concentrated in vacuo. Resulted syrup was poured into water (500 ml) and extracted three times with ethyl acetate. Combined organic extracts were dried over sodium sulfate, and the solvent was evaporated. The solid residue was then washed with a mixture of diethyl ether - hexane (3:7) to give the title iodide 1(a) (67 g, 81%) as a yellowish powder, m.p. : 82-84 °C.

b) 2-(4-N-Methylaminobutyl)-2*H*-naphth[1,8-*cd*]isothiazole 1,1-dioxide.

To a solution of N-methyltrifluoroacetamide (7.6 g, 60 mmol) in dimethylformamide (50 ml), was added in small portions sodium hydride (60% dispersion in oil) (2.0 g, 50 mmol). The solution was stirred for 20 min under nitrogen at room temp. Then iodo derivative 1(a) (19.4 g, 50 mmol) in dimethylformamide (50 ml) was slowly added dropwise over 20 min. Resulted mixture was stirred for 2 hours and then poured into water. Extraction with ethyl acetate and standard work-up gave a brown semi-solid which was subjected to flash chromatography (silica gel, ethyl acetate / hexane 3:7).yielding the corresponding trifluoroacetamide (9.3 g, 40 %) as a white powder, m.p.: 83-85°C. TLC: Rf = 0.5 (ethyl acetate / methylene chloride 5:95).

Solution of this amide (9.3 g, 24 mmol) in methanol (210 ml) was treated with 10% solution of potassium carbonate in methanol/water (7:3) (75 ml) and the reaction mixture stirred for 2 hours. Methanol was evaporated and the residue extracted with ethyl acetate. Standard workup gave amine 1(b) (5.3 g, 76%) as a green oil.

c)(R,S)-2-[4-[2-(1-Adamantyl)-2-oxoethyl]methylamino]butyl]-2H-naphth[1,8-*cd*]isothiazole 1,1-dioxide.

A solution of amine 1(b) (4.4 g, 15 mmol), 1-(bromoacetyl)-adamantane (4.11 g, 16 mmol) and anhydrous potassium carbonate (2.16 g, 15.6 mmol) in acetonitrile (60 ml) was heated under reflux over 3 hours. After cooling, the mixture was diluted with water and extracted with methylene chloride. The organic solution was dried over sodium sulfate and the solvent was evaporated. The residue was chromatographed (silica gel, ethyl acetate/methylene chloride 1:1, Rf = 0.4) to produce aminoketone 1(c) (4.0 g, 57%) as an orange oil.

d)(R,S)-1-(1-Adamantyl)-2-[N-methyl-N-[4-(2H-naphth[1,8-*cd*]isothiazol-2-yl)butyl]amino]ethanol S,S-dioxide, fumarate.

A solution of aminoketone 1(c) (4.0 g, 8.6 mmol) in ethanol (100ml) was treated with sodium borohydride (1.2 g, 30 mmol). The mixture was stirred for 4 hours at room temperature and then concentrated under reduced pressure. Water was added and the product was extracted with methylene chloride. The organic phase was washed twice with saturated aqueous solution of sodium bicarbonate and dried over sodium sulfate. Removal of solvent

under Removal of solvent under vacuum left the title aminoalcohol 1(d) (3.4 g, 85%) as an oil. TLC: Rf = 0.3 (methanol/ methylene chloride 5:95).
The aminoalcohol 1(d) (3.4 g, 7.3 mmol) on treatment with fumaric acid (1.16 g, 10 mmol) in isopropanol was converted into its fumarate salt (3.1 g, 73%), m.p.: 166-168°C. MS: 468 (M^+). Anal. Calc'd for $C_{31}H_{40}N_2O_7S$: C,63.68; H,6.90; N,4.79. Found: C,63.48; H,6.98; N,4.74.

EXAMPLE 2

(R,S)-2-[[1-[2-(1-Adamantyl)-2-oxoethyl]-4-piperidinyl]methyl]-2H-naphth[1,8-*cd*]isothiazole 1,1-dioxide, hydrochloride.

a) N-*tert*-Butoxycarbonyl isonipecotic acid.

Di-*tert*-Butyl dicarbonate (101.1 g, 464 mmol) was added dropwise to a stirred solution of isonipecotic acid (60 g, 464 mmol) and sodium hydroxide (37.6 g, 940 mmol) in a mixture of water (86 ml) and *tert*-butanol (176 ml). After the addition was completed, *tert*-butanol (100 ml) was added and the mixture was stirred for 3 hours at room temperature. The solution was diluted with water (200 ml) and extracted two times with pentane (150 ml). The aqueous phase was acidified with cooling with potassium hydrogen sulfate (70 g) and extracted with ethyl acetate. Standard workup gave N-Boc-protected iconipecotic acid 2(a) (102.3 g, 96%) as a white powder, m.p.: 144-146 °C.

b) N-*tert*-Butoxycarbonyl-4-hydroxymethylpiperidine.

To a cold (-15°C) solution of 2(a) (13.74 g, 60 mmol) in 1,2-dimethoxyethane (60 ml) was added N-methylmorpholine (6.66 ml, 60 mmol) followed by isobutyl chloroformate (8.16 ml, 60 mmol). After 10 min of stirring, the precipitate was filtered off and washed with 1,2-dimethoxyethane (60 ml). To the cooled (ice - salt bath) filtrate was slowly added a solution of sodium borohydride (3.42 g, 90 mmol) in water (30 ml). The mixture was stirred for 45 min., then diluted with water (800 ml) and extracted with of ethyl acetate (400 ml). Organic solution was washed with 0.05 N hydrochloric acid, water and finally with a saturated aqueous solution of sodium bicarbonate. The solution was dried and the solvent

evaporated to give the alcohol 2(b) (9.8 g, 75%) as a colorless oil which crystallized upon storing at room temperature, m.p.: 74-76°C.

c) N-*tert*-Butoxycarbonyl-4-[2-(2*H*-naphth[1,8-*cd*]isothiazol)methyl]-piperidine S,S-dioxide.

To an ice-cooled solution of alcohol 2(b) (26.8 g, 125 mmol) and triethylamine (19.1 ml, 137.5 mmol) in dry tetrahydrofuran (350 ml), methanesulfonyl chloride (11.3 ml, 137.5 mmol) was added dropwise. After stirring for 20 min, water was added and the reaction mixture was extracted with ethyl acetate. Combined organic extracts were washed with saturated aqueous solution of sodium bicarbonate, dried and evaporated producing N-*tert*-butoxycarbonyl-4-(methanesulfonyloxymethyl)piperidine in quantitative yield (36.6 g) as a white solid, m.p.: 72-74°C,

To the suspension of sodium hydride (60 % dispersion in oil) (5.94 g, 148.5 mmol) dry dimethylformamide (60 ml) was added a solution of 1,8-naphtosultam (27.7 g, 135 mmol) in dimethylformamide (80 ml) and the reaction mixture was stirred at room temperature under nitrogen for 20 min. Then sodium iodide (6.00 g, 40 mmol) was added followed by the above methanesulfonyloxymethyl-N-Boc-piperidine (36.6 g, 125 mmol) in dimethylformamide (80 ml) and the reaction was conducted at 80°C for 4 hours. After cooling, the reaction mixture was poured into water and extracted with ethyl acetate. The standard workup afforded a brownish oil which was subjected to column chromatography (silica gel, methylene chloride) giving the title compound 2(c) (43.5 g) in 80 % yield, m.p.: 112-114°C. TLC: Rf = 0.3 (ethyl acetate/hexane 3:7).

d) 4-[2-(2*H*-naphth[1,8-*cd*]isothiazol)methyl]piperidine S,S-dioxide.

N-Boc derivative 2(c) (36.0 g, 83.1 mmol) in ethyl acetate (400 ml) was treated with 4N hydrochloride solution in dioxane (83 ml) at room temperature overnight. Resulted white precipitate of 2(d) hydrochloride was filtered off and washed carefully with ethyl acetate. Quantitative yield, m.p. > 280 °C.

This hydrochloride was converted quantitatively into the free piperidine 2(d) by treatment with 0.5N sodium hydroxide aqueous solution and subsequent extraction with methylene chloride. A green oil was obtained which crystallized on standing at cold, m.p.: 188-190 °C.

e)(R,S)-2-[[1-[2-(1-Adamantyl)-2-oxoethyl]-4-piperidinyl]methyl]-2H-naphth[1,8-*cd*]isothiazole 1,1-dioxide, hydrochloride.

The aminoketone 2(e) was synthesized from piperidine 2(d) (11.2 g, 37 mmol) and 1-(bromoacetyl)adamantane (10.28 g, 40 mmol) following the procedure described in example 1(c). The crude product was isolated as an oil which crystallized on storing at room temp. Resulted orange powder was washed with ethanol and collected by filtration to give pure aminoketone 2(e) (13.6 g, 75%), m.p.: 168-170°C. TLC: Rf = 0.4 (ethyl acetate/ methylene chloride 1:1).

To the aminoketone 2(e) (1.5 g, 3.1 mmol) in ethanol (50 ml) was added 4N hydrogen chloride solution in dioxane (1.55 ml). Resulted solution was diluted with dry diethyl ether and left for crystallization. Precipitate was filtered off and dried under vacuum. Hydrochloride 2(e) (1.1 g, 69 %) was obtained as a grey powder, m.p.: 261-263°C . MS: 479 (M+1). Anal. Calc'd for $C_{28}H_{35}ClN_2O_3S$: C,65.29; H,6.85; N,5.44; Cl,6.88. Found : C,64.69; H,7.03; N,5.41; Cl,6.69.

EXAMPLE 3

(R,S)-2-[[1-[2-(1-Adamantyl)-2-oximinoethyl]-4-piperidinyl]methyl]-2H-naphth[1,8-*cd*]isothiazole 1,1-dioxide, hydrochloride.

The aminoketone 2(e) (1.46 g, 3 mmol) dissolved in a mixture of methanol (15 ml) and of tetrahydrofuran (5 ml) was reacted with hydroxylamine sulfate (0.540 g, 3.3 mmol) in presence of sodium acetate (0.540 g, 6.6 mmol) over 4 hours under reflux and then for 48 hours at room temperature. The single oxime product was formed; TLC: Rf = 0.6 (Ethyl acetate / methylene chloride 1 : 1). Reaction mixture was diluted with ethanol (30 ml), filtered and filtrate treated with 4M hydrogen chloride solution in dioxane (2.5 ml). The precipitate was filtered off and recrystallized from ethanol / diethyl ether (90:10) to give the title hydrochloride 3 (0.950 g, 57%) as a white crystalline powder,m.p.: 196-198°C. MS: 494 (M + 1). Anal. Calc'd for $C_{28}H_{36}ClN_3O_3S + 1.2\ H_2O$: C,60.95; H,7.02; N,7.62; Cl,6.43. Found : C,60.94; H,7.20; N,7.40; Cl,6.81.

EXAMPLE 4

(R,S)-1-(1-Adamantyl)-2-[4-(2H-naphth[1,8-*cd*]isothiazol-2-ylmethyl)piperidin-1-yl]ethanol S,S-dioxide, hydrochloride.

The aminoketone 2(e) (3.0 g, 6.1 mmol) was reduced following the method described in Example 1(d) yielding the aminoalcohol 4 (2.2 g, 74%) as a white powder, m.p.: 207-209°C. TLC: Rf = 0.5 (methanol/ methylene chloride 5:95). ^{1}H-NMR ($CDCl_3$,200 MHz) δ (ppm): 8.05 (d,1H); 7.9 (d,1H); 7.75 (dd,1H); 7.6-7.4 (m, 2H); 6.74 (d,1H); 3.7 (d,2H); 3.2 (dd,1H); 3.15-2.8 (m,4H); 2.4 (m,3H); 2.15-1.2 (m, 20 H).

The title hydrochloride salt was prepared from aminoalcohol 4 (2.0 g, 4.15 mmol) following procedure described in Example 2(e). Recrystallisation from methanol afforded pure product (1.2 g, 56 %) as a white crystalline solid, m.p.: 280°C (dec). MS: 315 (M - 165). Anal. Calc'd for $C_{28}H_{37}ClN_2O_3S$: C,65.03; H,7.21; N,5.42; Cl,6.86. Found: C,64.79; H,7.18; N,5.38; Cl,7.08.

EXAMPLE 5

(R,S)-1-(1-Adamantyl)-2-[4-(9-carbazolyl)methylpiperidin-1-yl]ethanol, hydrochloride.

a) N-*tert*-Butyloxycarbonyl-4-[9-(carbazolyl)methyl]piperidine.

The title compound 5(a) was prepared from carbazole (8.35 g, 50 mmol) and N-*tert*-Butyloxycarbonyl-4-(methanesulfonyloxymethyl) piperidine (15.0 g, 50 mmol) according to the method described in Example 2(c). Usual work-up of the reaction mixture provided a solid which was recrystallized from ethyl acetate / hexane to give pure product 5(a) (7.16 g, 39%), m.p.: 165-167°C. TLC: Rf = 0.2 (diethyl ether/ hexane 2:8).

b) 4-[9-(Carbazolyl)methyl]piperidine.

Removal of the *tert*-butyloxycarbonyl protecting group from 5(a) was performed as described in Example 2(d). The title compound 5(b) was obtained as a white syrup and was used in the next step without purification.

c) 9-[[1-[(1-Adamantyl)-2-oxoethyl]-4-piperidinyl]methyl]carbazole.

The amine 5(b) (3.6 g, 13.6 mmol) and 1-(bromoacetyl)adamantane (3.85 g, 15 mmol) were reacted together in acetonitrile containing potassium carbonate following the procedure described in Example 1(c). The aminoketone 5(c) (3.5 g, 59%) was isolated as a white powder, m.p.: 170-172°C. TLC: Rf = 0.6 (ethyl acetate/ methylene chloride 1:1).

d)(R,S)-1-(1-Adamantyl)-2-[4-(9-carbazolyl)methylpiperidin-1-yl]ethanol, hydrochloride.

Reduction of the aminoketone ketone 5(c) following the method described in Example 1(d) gave quantitatively the aminoalcohol 5(d) as a white solid, m.p.: 197-199°C. TLC: Rf = 0.3 (ethyl acetate / methylene chloride 1:1). The title hydrochloride salt was prepared according to the procedure described in Example 2(e) starting from aminoalcohol 5(d) (2.7 g, 6.1 mmol). Recrystallization from isopropyl alcohol / diethyl ether gave the salt (1.7 g, 58%) as a white powder, m.p.: 268-270°C. MS: 442 (M^+). Anal. Calc'd for $C_{30}H_{39}ClN_2OS$: C,75.21; H,8.20; N,5.85; Cl,7.40. Found: C,75.26; H,8.18; N,5.99; Cl,7.63.

EXAMPLE 6

(R,S)-1-(1-Adamantyl)-2-[N-methyl-N-[4-(2H-naphth[1,8-*cd*]isothiazol-2-yl)butyl]amino]ethylamine S,S-dioxide, tartrate.

a)2-[N-methyl-N-4-[(2-(1-Adamantyl)-2-methanesulfonyloxyethyl)-amino]butyl]-2H-naphth[1,8-*cd*]isothiazole 1,1-dioxide.

To a solution of aminoalcohol 1(d) (9.33 g, 20 mmol) in tetrahydrofuran (200 ml) cooled in an ice-water bath was added triethylamine (2.23 g, 22 mmol) followed by methanesulfonyl chloride (1.8 ml, 22 mmol). After stirring for 30 min., the mixture was quenched with water and extracted with methylene chloride. The combined organic extracts were washed with water, and saturated aqueous solution of sodium bicarbonate, then dried and the solvent was evaporated. A colorless viscous oil of methanesulfonate 6(a) was obtained in quantitative yield. TLC: Rf = 0.21 (ethyl acetate / hexane 3:7).

b)(R,S)-1-(1-Adamantyl)-1-azido-2-[N-methyl-N-[4-(2H-naphth[1,8-*cd*]isothiazol-2-yl)butyl]amino]ethylamine S,S-dioxide.

A mixture of methanesulfonate 6(a) (5.18 g, 9.5 mmol) and sodium azide (0.690 g, 10.6 mmol) in dry dimethylformamide (100 ml) was stirred overnight under nitrogen at room temperature. The reaction mixture was poured into water and extracted with ethyl acetate. The combined organic extracts were washed with water, dried and concentrated under vacuum. Purification of the residue by flash chromatography (silica gel, ethyl acetate/hexane 3:7) gave the title azide 6(b) (4.02 g, 86%) as an oil which crystallized as a white solid on standing at cold, m.p.: 24°C. TLC: Rf = 0.5 (ethyl acetate /hexane 1:1). IR (KBr): 2095 cm^{-1}. MS: 494 (M + 1). Anal. Calc'd for $C_{27}H_{35}N_5O_2S$: C,65.69; H,7.15; N,14.19. Found: C,65.41; H,7.23; N,13.95.

c)(R,S)-1-(1-Adamantyl)-2-[N-methyl-N-[4-(2H-naphth[1,8-*cd*]isothiazol-2-yl)butyl]amino]ethylamine S,S-dioxide, tartrate.

A solution of azide 6(b) (1.85 g, 3.7 mmol) in ethanol (100 ml) and tetrahydrofurane (20 ml) was hydrogenated with shaking over 10% Pd/C (2.2 g) at 2 kPa for 3 h at room temp. The slurry was filtered through *Celite* and solvents evaporated to give free diamine 6(c) (1.15 g, 65%) as a slightly yellow foam. TLC: Rf = 0.2 (methanol/methylene chloride 1:9).
Diamine 6(c) on treatment with (R,S) tartaric acid (2.2 equiv.) in ethanol was converted in 54% yield into the title tartrate salt 6(c), m.p.: 215-217°C.
Anal. Calc'd for $C_{31}H_{43}N_3O_8S + H_2O$: C,58.56; H,7.13; N,6.61. Found: C,58.37; H,6.89; N,6.61.

EXAMPLE 7

(R,S)-1-(1-Adamantyl)-N-methyl-2-[N-methyl-N-[4-(2H-naphth[1,8-*cd*]isothiazol-2-yl)butyl]amino]ethylamine S,S-dioxide, fumarate.

a)1-(1-Adamantyl)-N-methyl-N-trifluoroacetamido-2-[N-methyl-N-[4-(2H-naphth[1,8-*cd*]isothiazol-2-yl)butyl]amino]ethylamine S,S-dioxide.

A solution of methanesulfonate 6(a) (3.79 g, 6.9 mmol) in dry dimethylformamide (10 ml) was added to a pre-reacted over 20 min. mixture of N-methyltrifluoroacetamide (1.09 g, 8.4 mmol) and sodium hydride (60% suspension in oil) (0.280 g, 7 mmol) in dry dimethylformamide (10 ml) and then

heated overnight under nitrogen at 80 °C. After cooling, the reaction mixture was poured into water and extracted with ethyl acetate. The organic phase was dried and evaporated. The residue on chromatography (silica gel, ethyl acetate/hexane 1:3) gave the title compound 7(a) (2.89 g, 74%) as an oil. TLC: Rf = 0.8 (ethyl acetate/hexane 1:1).

b)(R,S)-1-(1-Adamantyl)-N-methyl-2-[N-methyl-N-[4-(2H-naphth[1,8-*cd*]isothiazol-2-yl)butyl]amino]ethylamine S,S-dioxide, fumarate.

The hydrolysis of the trifluoroacetamido group in 7(a) (2.89 g, 5.16 mmol) was performed in aqueous methanol in the presence of potassium carbonate (1.64 g, 11.9 mmol) as described in Example 1(b). After stirring overnight at room temperature, the reaction mixture was extracted with methylene chloride and worked-up as usual yielding free diamine 7(b) (1.76 g, 71 %) as an oil, TLC: Rf = 0.3 (methanol/methylene chloride 1:9).
Following the usual procedure (Examples 1(d) and 6(c)) the title fumarate salt was crystallized from ethanol in 42% yield. M.p.: 168-170°C. Anal. Calc'd for $C_{32}H_{43}N_3O_6S$: C,64.30; H,7.25; N,7.03. Found: C,64.03; H,7.30; N,7.08.

EXAMPLE 8

(R,S)-2-(1-Adamantyl)-N-methyl-N-[4-(2H-naphth[1,8-*cd*]isothiazol-2-yl)butyl]-2-pyrrolidin-1-ylethylamine S,S-dioxide, fumarate.

A mixture of mesylate 6(a) (2.72 g, 5 mmol), pyrrolidine (0.83 ml, 10 mmol), anhydrous potassium carbonate (1.14 g, 8.2 mmol), and sodium iodide (0.225 g, 1.5 mmol) was stirred and heated under reflux over 2 hours under nitrogen. After cooling, the mixture was diluted with water and extracted with methylene chloride. Standard work-up furnished free diamine 8 (1.9 g, 73%) as a yellow oil, TLC: Rf = 0.2 (methanol/methylene chloride 1:9).
The fumarate salt 8 was crystallized from ethanol in 44% yield following the usual procedure (Examples 1(d) and 6(c)). M.p.: 190-191°C. Anal. Calc'd for $C_{35}H_{47}N_3O_6S$: C,65.91; H,7.43; N,6.59. Found: C,65.79; H,7.48; N,6.67.

EXAMPLE 9

(R,S)-2-[4-[N-[2-(1-Adamantyl)-2-methoxyethyl]-N-methylamino]butyl]-2H-naphth[1,8-*cd*]isothiazole 1,1-dioxide, tartrate.

The methanolysis of mesylate 6(a) (2.72 g, 4.8 mmol) was conducted in boiling methanol (70 ml) for 5 hours. After evaporation of the solvent, the residue was taken in methylene chloride and resulted solution washed with 0.025M aqueous sodium hydroxide, water and saturated aqueous sodium bicarbonate. The organic phase was dried and concentrated and the residual material purified by chromatography (silica gel, ethyl acetate/methylene chloride /methanol 10:10:1) to give methyl ether 9 (0.770 g, 33 %) as an oil. TLC: Rf = 0.3 (methylene chloride/methanol 95:5).
According to the standard procedure (Examples 1(d) and 6(c)) the tartrate salt was crystallized from ethanol as a white solid, m.p.: 124-126°C. MS: 303 (M-179). Anal. Calc'd for $C_{32}H_{44}N_2O_9S$ + 1/3 H_2O: C,60.14; H,6.99; N,4.38. Found : C,60.14; H,7.18; N, 4.59.

EXAMPLE 10

(R,S)-1-(1-Adamantyl)-2-[N-methyl-N-[4-[5H-phenanthridin-6-oxo-5-yl]butyl]-amino]ethanol, hydrochloride.

a) 4-(N-*tert*-Butoxycarbonyl-N-methylamino)butyric acid.

This compound was prepared from 4-(N-methylamino)butyric acid hydrochloride (23 g, 150 mmol) and di-*tert*-butyl dicarbonate (32.7 g, 150 mmol) according to the method described in Example 2(a). The product 10(a) (31 g, 95%) was obtained as an oil.

b) N-*tert*-Butoxycarbonyl-N-methyl-4-hydroxybutylamine.

Reduction of the carboxylic acid 10(a) (31 g, 142 mmol) *via* its mixed carboxylic-carbonic anhydride, following the procedure presented in Example 2(b), produced alcohol 10(b) (19.5 g, 64%) as an oil.

c) N-Methyl-N-[(5H-phenanthridin-6-oxo-5-yl)butyl]amine.

Following the procedure described in Example 2(c) the alcohol 10(b) was first converted into the mesylate in 98% yield. Reaction of the above mesylate (5.6 g, 20 mmol) with dihydro(5H)-phenanthridinone (4.3 g, 22 mmol) in the presence of sodium hydride in dimethylformamide furnished N-tert-butoxycarbonyl-N-methyl-N-[(5H-phenanthridin-6-oxo-5-yl)butyl]amine (4.5 g, 59%), TLC: Rf = 0.35 (ethyl acetate /hexane 3:7). Removal of the N-tert-butoxycarbonyl protecting group from above N-Boc derivative (4.4 g, 11.4 mmol) was performed following the procedure 2(d). The title amine 10(c) (2.8 g, 88%) was obtained as a colorless oil.

d)5-[4-[2-(1-Adamantyl)-2-oxoethyl]methylamino]butyl]-6(5H)-phenanthridinone.

The amine 10(c) (2.8 g, 10 mmol) and 1-(bromoacetyl) adamantane (2.83 g, 11 mmol) were reacted together, according to procedure presented in Example 1(c), to produce the title ketone 10(d) (3.31 g, 73%) as a yellow oil. TLC: Rf = 0.5 (ethyl acetate/ methylene chloride 1:1).

e) (R,S)-1-(1-Adamantyl)-2-[N-methyl-N-[4-(5H-phenanthridin-6-oxo-5-yl)butyl]amino]ethanol, hydrochloride.

Ketone 10(d) (3.2 g, 7.0 mmol) was reduced with sodium borohydride in ethanol, following the procedure described in Example 1(d), yielding the free aminoalcohol 10(e) (3.0 g, 94%) as an oil. TLC: Rf = 0.3 (methanol / methylene chloride 1:9).

The title hydrochloride was prepared according to the procedure described in Example 2(e). Starting from aminoalcohol 10(e) (2 g, 4.3 mmol) and after recrystallization from ethanol / diethyl ether the salt 10(e) (1.4 g, 63%) was obtained as a white hygroscopic powder; m.p.: 127-129°C. MS: 293 (M - 165). Anal. Calc'd for $C_{30}H_{39}ClN_2O_2 + H_2O$: C,70.22; H,8.05; N,5.46; Cl,6.91. Found: C,70.48; H,7.95; N,5.59; Cl,7.27.

EXAMPLE 11

(R,S)-1-(1-Adamantyl)-2-[N-methyl-N-[4-(6H-dibenzo[c,e][1,2]thiazin-6-yl)butyl]amino]ethanol S,S-dioxide.

a) N -Methyl-N-[4-[6-(6H-dibenzo[*ce*][1,2]thiazin)]butyl]amine S,S-dioxide.

The synthesis of amine 11(a) was performed following the sequence of reactions described in Example 10(c). Alkylation of 6*H*-dibenzo[*ce*]-1,2-thiazine-5,5-dioxide (4.16 g, 18 mmol) with mesylate of 10(b) (5.06 g, 18 mmol) gave N-*tert*-butoxycarbonyl-N-methyl-N-[4-[6-(6H-dibenzo[*ce*][1,2]thiazin)]butyl]amine S,S-dioxide (6.45 g, 77%) as a viscous oil. TLC: Rf = 0.3 (ethyl acetate /hexane 3:7). Next, removal of N-*tert*-butoxycarbonyl group and basic work-up furnished the title amine 11(a) (4.3 g, 76% overall yield) as a yellowish oil.

b) (R,S)-1-(1-Adamantyl)-2-[N-methyl-N-[4-(6H-dibenzo[c,e] [1,2]thiazin-6-yl)butyl]amino]ethanol S,S-dioxide.

To a warm solution of the amine 11(a) (0.886 g, 2.8 mmol) in ethanol (15 ml) was added (1-adamantyl)ethylene oxide (0.500 g, 2.8 mmol). The mixture was refluxed over 48 hours under nitrogen. After cooling, the solvent was evaporated and the residue subjected to column chromatography (silica gel, methanol / methylene chloride 1:20) to give the title aminoalcohol 11(b) (1 g, 72 %) as a white foam. TLC: Rf = 0.25 (methanol / methylene chloride 1:20). Anal. Calc'd for $C_{29}H_{38}N_2O_3S$ + 0.5 H_2O: C,69.09; H,7.74; N,5.55. Found: C,68.79; H,7.70; N, 5.50.
(1-Adamantyl)ethylene oxide was prepared according to Shiryaev A.K. *et al.*, *Khim. Farm. Zh.*, 1990, *24*, 23-25.

EXAMPLE 12

(R,S)-1-(1-Adamantyl)-2-[4-(2H-naphth[1,8-*cd*]isothiazol-2-ylmethyl)piperidin-1-yl]ethylamine S,S-dioxide, tartrate.

a)1-(1-Adamantyl)-1-methanesulfonyloxy-2-[4-(2H-naphth[1,8-*cd*]isothiazol-2-ylmethyl)piperidin-1-yl]ethane S,S-dioxide.

Following procedure described in Example 6(a) reaction of methanesulfonyl chloride with aminoalcohol 4 produced the title mesylate 12(a) in 96% yield as a white solid, m.p.: 175.5-176.5°C. TLC: Rf = 0.21 (ethyl acetate/hexane 3:7).

b) 1-(1-Adamantyl)-1-azido-2-[4-(2H-naphth[1,8-*cd*]isothiazol-2-ylmethyl)piperidin-1-yl]ethane S,S-dioxide.

Reaction of mesylate 12(a) with sodium azide in dimethylformamide was performed in a similar manner to that described in Example 6(b) and afforded azide 12(b) in 45% yield as a white solid, m.p.: 170.5-170.6°C. TLC: Rf = 0.7 (ethyl acetate/hexane 1:1). IR (KBr): 2096 cm^{-1}.

c)(R,S)-1-(1-Adamantyl)-2-[4-(2H-naphth[1,8-*cd*]isothiazol-2-ylmethyl)-piperidin-1-yl]ethylamine S,S-dioxide, tartrate.

Following procedure described in Example 6(c) reduction of azide 12(b) gave diamino compound 12(c) in 36% yield as a viscous oil. TLC: Rf = 0.2 (methanol / methylene chloride 1:9).

The title tartrate salt 12 was crystallized in a usual way (exp. 1(d) and 6(c)) from ethanol in 40% yield as a white powder, m.p.: 189-190°C. Anal. Calc'd for $C_{32}H_{43}N_3O_8S$ + 1.2 H_2O: C,59.01; H,7.03; N,6.45. Found: C,58.74; H,6.66; N, 6.40.

EXAMPLE 13

(R,S)-1-(1-Adamantyl)-N-methyl-2-[4-(2*H*-naphth[1,8-*cd*]isothiazol-2-ylmethyl)piperidin-1-yl]ethylamine S,S-dioxide, maleate.

a) 1-(1-Adamantyl)-N-methyl-N-trifluoroacetamido-2-[4-(2*H*-naphth[1,8-*cd*]isothiazol-2-ylmethyl)piperidin-1-yl]ethylamine S,S-dioxide.

Reaction of N-methyltrifluoroacetamide with mesylate 12(a), performed as described in Example 7(a), produced compound 13(a) in 65% yield as an oil.

b) (R,S)-1-(1-Adamantyl)-N-methyl-2-[4-(2*H*-naphth[1,8-*cd*]isothiazol-2-ylmethyl)piperidin-1-yl]ethylamine S,S-dioxide, maleate.

Hydrolysis of the trifluoroacetamide 13(a) was conducted as previously described in Example 7(b) and gave the title free diamine in 65% yield as a solidified foam. TLC: Rf = 0.5 (methanol / methylene chloride 1:9).

On the usual treatment with an excess of maleic acid in ethanol / diethyl ether diamine 13(b) was converted into its maleate salt in 50% yield. White

powder, m.p.: 191-193°C. Anal. Calc'd for $C_{33}H_{43}N_3O_6S$ + 0.5 H_2O: C,64.08; H,7.11; N,6.80. Found: C,64.08; H,7.11; N,6.90.

EXAMPLE 14

(R,S)-2-[1-[2-(1-Adamantyl)-2-pyrrolidin-1-ylethyl]piperidin-4-ylmethyl]-2H-naphth[1,8-*cd*]isothiazole 1,1-dioxide, fumarate.

Reaction of mesylate 12(a) with pyrrolidine, conducted as described in Example 8, afforded diamine 14 in 70% yield as a white solidified foam. TLC: Rf = 0.3 (methanol / methylene chloride 1:9).
The fumarate salt was prepared in ethanol, according to the usual procedure, in 68% yield as a slightly brown powder, m.p.: 194-196°C. Anal. Calc'd for $C_{36}H_{47}N_3O_6S$ + 0.25 H_2O: C,66.05; H,7.26; N,6.42. Found: C,65.92; H,7.31; N,6.49.

EXAMPLE 15

(R,S)-2-[1-[2-(1-Adamantyl)-2-morpholin-4-ylethyl]piperidin-4-ylmethyl]-2H-naphth[1,8-*cd*]isothiazole 1,1-dioxide, dihydrochloride.

Following procedure described in Example 8, reaction of mesylate 12(a) and morpholine gave diamine 15 in 71% yield as a white solidified foam. TLC: Rf = 0.3 (methanol/methylene chloride 1:9).
The dihydrochloride salt was prepared in 61% yield, according to the procedure 2(e), as a white hygroscopic solid, m.p.: 182-184°C. Anal. Calc'd for $C_{32}H_{45}Cl_2N_3O_3S$ + H_2O: C,59.99; H,7.39; N,6.56. Found: C,60.41; H,7.74; N,6.64.

EXAMPLE 16

(R,S)-2-[1-[2-(1-Adamantyl)-2-(4-methyl)piperazin-1-ylethyl]piperidin-4-ylmethyl]-2H-naphth[1,8-*cd*]isothiazole 1,1-dioxide, hydrochloride.

Mesylate 12(a) and N-methylpiperazine were reacted under conditions analogous to Example 8 and gave the title triamine 16 in 86% yield as a white solid, m.p.: 114.9-115.5°C. TLC: Rf = 0.3 (methanol/methylene chloride 1:9).

The hydrochloride salt was prepared in 48 % yield, according to the procedure 2(e), as a white solid, m.p.: 213.5-214.3°C. Anal. Calc'd for $C_{33}H_{46}N_4O_2S$ + 2.8 HCl +1.5 H_2O: C,57.19; H,7.58; N,8.09; Cl,14.35. Found: C,57.26; H,7.73; N,8.07; Cl,14.23.

EXAMPLE 17

(R,S)-1-(1-Adamantyl)-N,N-diethyl-2-[4-(2H-naphth[1,8-*cd*]isothiazol-2-ylmethyl)piperidin-1-yl]ethylamine S,S-dioxide, fumarate.

Mesylate 12(a) and diethylamine were reacted together, under conditions described in Example 8, to give diamine 17 in 46% yield as an oil. TLC: Rf = 0.3 (methanol / methylene chloride 1:9).

The fumarate salt was crystallized from ethanol, according to the usual procedure, in 48% yield as a white solid, m.p.: 221.5-222.3°C. Anal. Calc'd for $C_{36}H_{49}N_3O_6S$ + 1/3 H_2O: C,65.75; H,7.55; N,6.39. Found: C,65.77; H,7.66; N,6.39.

EXAMPLE 18

(R,S)-1-(1-Adamantyl)-N-allyl-N-methyl-2-[4-(2H-naphth[1,8-*cd*]isothiazol-2-ylmethyl)piperidin-1-yl]ethylamine S,S-dioxide, fumarate.

Following typicall procedure (Example 8), reaction of mesylate 12(a) with N-methylallylamine furnished diamino compound 18 in 20 % yield as a white solidified foam. TLC: Rf = 0.5 (ethyl acetate).

Diamine 18, on the usual treatment with fumaric acid in ethanol, gave the title salt 18 in 49% yield as a white solid, m.p.: 191.7-192.8°C. Anal. Calc'd for $C_{36}H_{47}N_3O_6S$ + H_2O: C,64.74; H,7.40; N,6.29. Found: C,64.61; H,7.26; N,6.14.

EXAMPLE 19

(+)-(S)-1-(1-Adamantyl)-2-[4-(2H-naphth[1,8-*cd*]isothiazol-2-ylmethyl)piperidin-1-yl]ethanol S,S-dioxide.

Reaction of 4-[2-(2H-naphth[1,8-*cd*]isothiazol-1,1-dioxide)methyl] piperidine 2(d) (0.151 g, 0.5 mmol) with (+)-S-(1-adamantyl)ethylene oxide (0.089 g, 0.5 mmol) was conducted following procedure described in Example 11(b), but over 72 hrs. Column chromatography (silica gel, methylene chloride / methanol 20:1) gave pure aminoalcohol 19 (0.155 g, 65%) as a solidified foam, m.p.: 202.5 - 204.5°C. $[a]_D^{20}$ = +24.7° (c 1.3, $CHCl_3$). ^{1}H-NMR ($CDCl_3$): identical to that of a racemic aminoalcohol 4.
The (+)-S-(1-adamantyl)ethylene oxide ($[a]_D^{20}$ = + 13.3° (c 1.6, $CHCl_3$)) was prepared according to De Ninno M.P. *etal.* (*J.Org.Chem.*, 1992, *57*, 7115-7118), but starting with the opposite enantiomer of the catalyst.

EXAMPLE 20

(-)-(R)-1-(1-Adamantyl)-2-[4-(2H-naphth[1,8-*cd*]isothiazol-2-ylmethyl)piperidin-1-yl]ethanol S,S-dioxide.

Following procedure 11(b), (-)-R-(1-adamantyl)ethylene oxide (0.500 g, 2.8 mmol) and piperidine 2(d) (0.845 g, 2.8 mmol) were reacted together, but over 54 hrs. Purification by column chromatography furnished aminoalcohol 20 (0.710 g, 55%) as a white solid, m.p.: 204.5 - 205.5°C. $[a]_D^{20}$ = - 29.3° (c 1, $CHCl_3$). ^{1}H-NMR ($CDCl_3$): identical to that of aminoalcohol 4.
The (-)-R-(1-adamantyl)ethylene oxide ($[a]_D^{20}$ = - 14.7° (c 1, $CHCl_3$)) was prepared according to De Ninno M.P. *etal.* (*J. Org. Chem.*, 1992, *57*, 7115-7118).

EXAMPLE 21

(R,S)-2-[1-[2-(1-Adamantyl)-2-methoxyethyl]piperidin-4-ylmethyl]-2H-naphth[1,8-*cd*]isothiazole 1,1-dioxide, hydrochloride.

Sodium hydride (60 % dispersion in oil) (0.6 g, 14 mmol) was added to a solution of aminoalcohol 4 (3.0 g, 2.7 mmol) in dry tetrahydrofuran (60 ml) at room temperature under nitrogen, and the resulted mixture was stirred for 20 min. Next, dimethylsulfate (0.6 ml, 2.7 mmol) was added and stirring continued overnight. Reaction was quenched with water (50 ml) and extracted with methylene chloride. The combined organic extracts were dried and evaporated. The residue was chromatographed (silica gel, methylene chloride / ethyl acetate 6:4, then 1:1) to give methyl ether 21 (1.0 g, 30%) as a white solid, m.p.: 169-171°C. TLC: Rf = 0.65 (methylene chloride /ethyl acetate 7:3). ^{1}H-NMR ($CDCl_3$): 8.06 (d,1H); 7.97 (d,1H); 7.75 (dd,1H); 7.53 (dd,1H); 7.45 (d,1H); 6.74 (d,1H); 3.68 (d,2H); 3.48 (s,3H); 3.04-2.95 (m,2H); 2.73 (dd,1H); 2.49-2.33 (m,2H); 2.10-1.34 (m, 22 H). MS: 315(M-179). Anal. Calc'd for $C_{29}H_{38}N_2O_3S$: C,70.41; H,7.74; N,5.66. Found: C,70.17; H,7.84; N, 5.60.

The hydrochloride salt was prepared according to the procedure 2(e) as a white solid, m.p.: 198-205 °C. Anal.Calc'd for $C_{29}H_{38}N_2O_3S$ + HCl + 0.5 H_2O: C,64.44; H,7.41; N,5.18; Cl,6.57. Found: C,64.09; H,7.35; N,4.96; Cl,6.38.

EXAMPLE 22

(+)-(S)-2-[1-[2-(1-Adamantyl)-2-methoxyethyl]piperidin-4-ylmethyl]-2H-naphth[1,8-*cd*]isothiazole 1,1-dioxide, hydrochloride.

The O-methylation of the (+)-S-aminoalcohol 19 was performed as described in the Example 21. Methyl ether 22 was obtained in 42 % yield. ^{1}H-NMR ($CDCl_3$): identical to that of racemic methyl ether 21.

The hydrochloride salt was prepared according to the procedure 2(e) as a white hygroscopic foam. Anal. Calc'd for $C_{29}H_{38}N_2O_3S$ + HCl + 0.5 H_2O: C,64.44; H,7.41; N,5.18; Cl,6.57. Found: C,64.29; H,7.61; N,5.11; Cl, 6.56 . $[a]_D^{20}$ = + 13.2° (c 1, $CHCl_3$).

EXAMPLE 23

(-)-(R)-2-[1-[2-(1-Adamantyl)-2-methoxyethyl]piperidin-4-ylmethyl]-2H-naphth[1,8-*cd*]isothiazole 1,1-dioxide, hydrochloride.

The O-methylation of the (-)-R-aminoalcohol 20 was performed as described in the Example 21. Methyl ether 23 was obtained in 55 % yield. ^{1}H-NMR ($CDCl_3$): identical to that of racemic methyl ether 21.

The hydrochloride salt was prepared according to the procedure 2 (e) as a white hygroscopic foam. Anal.Calc'd for $C_{29}H_{38}N_2O_3S$ + HCl + H_2O: C,63.38; H,7.47; N,5.10; Cl,6.47. Found: C,63.60; H,7.51; N,5.13; Cl,6.55.
$[a]_D^{20}$ = - 17.3° (c 1, $CHCl_3$).

EXAMPLE 24

(R,S)-2-[1-[2-(1-Adamantyl)-2-ethoxyethyl]piperidin-4-ylmethyl]-2H-naphth[1,8-*cd*]isothiazole 1,1-dioxide, fumarate.

A solution of the mesylate 12(a) (2.5 g, 4.5 mmol) in ethanol (50 ml) was heated under reflux for 2 hrs. After evaporation of the solvent, the residue was diluted with methylene chloride and treated with 0.025 M aqueous sodium hydroxyde, then water and saturated aqueous sodium bicarbonate. The organic phase was dried and concentrated. Residue was chromatographed (silica gel, methylene chloride / methanol 95:5) to give a white solid (0.76 g) which was recrystallized from ethyl acetate yielding ethyl ether 24 (0.55 g, 31%). M.p.: 162.3-163.3 °C. TLC: Rf = 0.2 (ethyl acetate / hexane 3:7).
^{1}H-NMR ($CDCl_3$): 8.06 (d,1H); 7.97 (d,1H); 7.75 (dd,1H); 7.53 (dd,1H); 7.45 (d,1H); 6.74 (d,1H); 3.8 (m,1 H); 3.68 (d,2H); 3.5 (m,1H); 3.1 (m,2H); 2.5 (m,2H); 2.05-1.5 (m, 24 H); 1.2 (t, 3 H).
The fumarate salt 24 was crystallized in a usual way, from ethanol in 64% yield as a white solid, m.p.: 206.7-207.4°C. Anal. Calc'd for $C_{34}H_{44}N_2O_7S$: C,65.36; H,7.10; N,4.48. Found: C,65.25; H,6.99; N,4.59.

EXAMPLE 25

(-)-2-[1-[2-(1-Adamantyl)-2-ethoxyethyl]piperidin-4-ylmethyl]-2H-naphth[1,8-*cd*]isothiazole 1,1-dioxide.

a) (-)-1-(1-Adamantyl)-1-camphosulfonyloxy-2-[4-(2H-naphth[1,8-

cd]isothiazol-2-ylmethyl)piperidin-1-yl]ethane S,S-dioxide.

The sulfonylation of the racemic aminoalcohol 4 (5.8 g, 12.08 mmol) with (1S)-(+)-10-camphorsulphonyl chloride (4.54 g, 18 mmol) was conducted in tetrahydrofuran (180 ml) in the presence of triethylamine (2.52 ml, 18 mmol). After the usual work-up, the mixture of diastereoisomers was separated by chromatography (silica gel, ethyl acetate / hexane 2:8). The camphosulfonic ester (-)-25(a) (1.18 g, 14.2 %) was eluted first (Rf = 0.46) and crystallized as a white solid, mp : 201-203 °C. $[a]_D^{24}$ = - 40° (c 1, $CHCl_3$).

b)(-)-2-[1-[2-(1-Adamantyl)-2-ethoxyethyl]piperidin-4-ylmethyl]-2H-naphth[1,8-*cd*]isothiazole 1,1-dioxide

A solution of the (-)-camphosulfonate 25(a) (0.500 g, 0.72 mmol) in of ethanol (50 ml) was heated under reflux for 3 hrs. After evaporation of the solvent, the residue was diluted with methylene chloride and treated with 0.025 M aqueous sodium hydroxide, then water and saturated aqueous sodium bicarbonate. The organic phase was dried, concentrated under vacuum and the resulting solid was purified by silicagel chromatography (eluent : methylene chloride /methanol 95:5) to give 200 mg (54.5 %) of a white solid. mp : 159.3-161 °C. TLC: Rf = 0.2 (ethyl acetate/hexane 3:7).
The ^{1}H-NMR ($CDCl_3$) was identical to that of the Example 24.
$[a]_D^{24}$ = 27° (c 1, CHCl3).

EXAMPLE 26

(R,S)-1-(1-Adamantyl)-1-methyl-2-[4-(2H-naphth[1,8-*cd*]isothiazol-2-ylmethyl)piperidin-1-yl]ethanol S,S-dioxide, hydrochloride.

Methyl lithium (1.4 M in ether, 6.0 ml, 8.4 mmol) was slowly added dropwise at 0°C to a stirred suspension of aminoketone 2(e) (4.0 g, 8.4 mmol) in tetrahydrofuran (80 ml). The suspension gradually changed to a pink solution. Additional methyl lithium (1.4 M in ether, 2.0 ml, 2.8 mmol) was added. Resulted red solution was stirred for 3 h and during that time the red colour disappeared. Reaction was quenched with water (20 ml) followed by ethyl acetate (100 ml) and brine (30 ml). The layers were separated and the aqueous one was extracted with methylene chloride (50 ml). The combined

organic phases were dried and concentrated. Residue was purified by column chromatography (silica gel, hexane / ethyl acetate 6:4, then methylene chloride /ethyle acetate 1:1) to afford aminoalcohol 26 (0.5 g, 12 %) as a white solid, m.p.: 78-81°C. TLC: Rf = 0.66 (hexane / ethyl acetate 6:4). MS: 315 (M-179). Anal. Calc'd for $C_{29}H_{38}N_2O_3S$: C,70.41; H,7.74; N,5.66. Found: C,70.14; H, 7.75; N, 5.66.

The hydrochloride salt was prepared, according to the general procedure 2(e), as a white solid, mp : 271.2-272 °C. Anal. Calc'd for $C_{29}H_{38}N_2O_3S$ + HCl +1.1 H_2O: C,63.22; H,7.54; N,5.08; Cl,6.43. Found: C,63.26; H,7.48; N,5.01; Cl,6.25.

EXAMPLE 27

(R,S)-1-Cyclohexyl-2-[4-(2H-naphth[1,8-*cd*]isothiazol-2-ylmethyl)piperidin-1-yl]ethanol S,S-dioxide, hydrochloride.

a) 1-Cyclohexyl-2-chloroethan-1-one.

A solution of cyclohexanecarbonyl chloride (2.0 ml, 15 mmol) in diethyl ether (6 ml) was slowly added at room temp. over 30 min. to the etheral solution of diazomethane (prepared from Diazald (*Aldrich*) (10.0 g, 46.7 mmol) according to Hudlicky M. *J. Org. Chem.*, 1980, *45*, 5377-5378). The reaction was conducted for 1 h. Next, hydrogen chloride was bubbled into the reaction mixture at 0°C for 20 min. Then water (50 ml) was added, layers were separated and the etheral one was washed with saturated aqueous sodium carbonate solution. Organic solution was dried and evaporated. Residual liquid was treated with saturated aqueous sodium bicarbonate solution and stirred for 2 h. Mixture was extracted with ether, combined extracts were dried and evaporated to give fairly pure chloromethylketone 27(a) (1.1 g, 46%) as a yellow liquid.

b)2-[(1-(2-Cyclohexyl-2-oxoethyl)-4-piperidinyl)methyl]-2H-naphth[1,8-*cd*]isothiazole 1,1-dioxide.

A mixture of chloromethylketone 27(a) (1.4 g, 8.3 mmol), hydrochloride 2(d) (2.5 g, 7.3 mmol), anhydrous potassium carbonate (1.2 g, 8.3 mmol) and sodium iodide (1.4 g, 8.3 mmol) in 30 ml of acetonitrile was vigorously stirred under reflux for 3 h. After cooling, water (60 ml) was added, resulted mixture stirred for 20 min., and then extracted twice with methylene

chloride (100 ml). The combined organic layers were dried and evaporated to give crude aminoketone 27(b) (3.0 g, 100%) which was sufficiently pure for the next step.

c)(R,S)-1-Cyclohexyl-2-[4-(2H-naphth[1,8-*cd*]isothiazole-2-ylmethyl)piperidin-1-yl]ethanol S,S-dioxide, hydrochloride.

Reduction of the aminoketone 27(b) (3.0 g, 7 mmol), according to the method described in Example 1(d), followed by purification by column chromatography (silica gel, methylene chloride / ethyl acetate 7:3, then 1:1) gave aminoalcohol 27(c) (1.9 g, 63%) as a white solid, m.p.: 148-150 °C. TLC: Rf = 0.12 (methylene chloride / ethyl acetate (98:2). MS: 429 (M+1). Anal. Calc'd for $C_{24}H_{32}N_2O_3S$: C,67.26; H,7.53; N,6.54. Found: C,67.11; H,7.57; N,6.40.

The hydrochloride salt was prepared according to the usual procedure 2(e) as a white solid, m.p.: 262.7-264 °C. Anal.Calc'd for $C_{24}H_{32}N_2O_3S$ + 1.75 HCl: C,58.54; H,6.91; N,5.69; Cl,12.60. Found: C,58.38; H,6.89; N,5.64; Cl,12.69.

EXAMPLE 28

(R,S)-1-(1-Adamantyl)-2-[4-(2-chlorophenothiazin-10-ylmethyl)piperidin-1-yl]-ethanol, hydrochloride.

a) N-*tert*-Butoxycarbonyl-4-[10-(2-chlorophenothiazyl)methyl]piperidine.

Compound 28(a) was prepared from 2-chlorophenothiazine (5 g, 21.4 mmol) and N-*tert*-butoxycarbonyl-4-(methanesulphonyloxymethyl) piperidine (15.0 g, 50 mmol) according to the method described in Example 2(c), but reaction was performed in boiling p-xylene over 40 hrs and without addition of sodium iodide. The crude product, obtained after usual extractive work-up of the reaction mixture, was chromatographed (silica gel, ethyl acetate / hexane 1:9) yielding 28(a) (3.5 g, 38%) as a slightly yellow foam.

b) 4-[10-(2-Chlorophenothiazyl)methyl]piperidine hydrochloride.

Removal of the N-*tert*-butoxycarbonyl protecting group from 28(a) was performed in the presence of hydrogen chloride as described in Example 2(d). The title piperidine hydrochloride 28(b) was obtained in 96% yield as a white solid, m.p.: 248-250 °C.

c)10-[(1-(2-(1-Adamantyl)-2-oxoethyl)-4-piperidinyl)methyl]-2-chloro-phenothiazine.

Hydrochloride 28(b) (3.19 g, 8.69 mmol) and 1-(bromoacetyl) adamantane (2.38g, 9.25 mmol) were reacted in boiling acetonitrile (35 ml) in the presence of anhydrous potassium carbonate (1.25 g, 9.04 mmol) following the method descrbed in Example 1(c). The aminoketone 27(c) (3.4 g, 77 %) was obtained as a cream colored solid, m.p.: 178-181 °C.

d)(R,S)-1-(1-Adamantyl)-2-[4-(2-chlorophenothiazin-10-ylmethyl)-piperidin-1-yl]ethanol, hydrochloride.

The aminoketone 28(c) was reduced according to the method described in the Example 1(d). Purification by column chromatography (silica gel, ethyl acetate / methylene chloride 5:95, then 10:90) afforded aminoalcohol 28(d) in 90% yield as a white solid, m.p.: 215-217 °C. TLC: Rf = 0.5 (ethyl acetate / hexane 1:1). MS: 343 (M-165). Anal. Calc'd for $C_{30}H_{37}ClN_2OS$: C,70.77; H,7.32; N,5.50. Found: C,71.07; H,7.54; N,5.45.
The title hydrochloride salt was prepared following the usual procedure 2(e) as a white solid, m.p.: 256-258 °C. Anal. Calc'd for $C_{30}H_{37}ClN_2O_1S$ + HCl: C,66.04; H,7.02; N,5.13; Cl,13.00. Found: C,65.86; H,6.97; N,5.10; Cl,13.02.

EXAMPLE 29

(R,S)-1-(1-Adamantyl)-2-[4-(phenothiazin-10-ylmethyl)piperidin-1-yl]ethanol, hydrochloride.

a) N-*tert*-Butoxycarbonyl-4-[(10-phenothiazyl)methyl]piperidine.

Compound 29(a) was prepared from phenothiazine (4.4 g, 22 mmol) and N-*tert*-Butoxycarbonyl-4-(methanesulphonyloxymethyl)piperidine (6.0 g, 20 mmol) according to the method described in Example 2(c). Column chromatography (silica gel, ethyl acetate / hexane 15:85, Rf = 0.3) gave 29(a) (8 g, 97%) as a brown solid, m.p.: 104-106 °C.

b) 4-[(10-Phenothiazyl)methyl]piperidine.

Removal of the N-*tert*-butoxycarbonyl protecting group in 29(a) was performed with hydrogen chloride, as described in Example 2(d), to produce 29(b) hydrochloride salt in 87 % yield as a white solid. m.p.:137-139 °C.

The basic work-up gave the title free amine 29(b) in 95% yield as a white solid, m.p.: 83-85 °C.

c)10-[[1-[2-(1-Adamantyl)-2-oxoethyl]-4-piperidinyl]methyl]-phenothiazine.

Amine 29(b) (4.7 g, 15 mmol) and 1-(bromoacetyl)adamantane (4.8 g, 18 mmol) were converted to the aminoketone 29(c) (5.9 g, 83%), according to the method described in Example 1(c). A cream colored solid was obtained, m.p.: 177-179°C. TLC: Rf = 0.5 (ethyl acetate / methylene chloride 1:1).

d) (R,S)-1-(1-Adamantyl)-2-[4-(phenothiazin-10-ylmethyl)piperidin-1-yl]-ethanol, hydrochloride.

Aminoketone 29(c) was reduced according to the procedure described in the Example 1(d). Crude product was recrystallized from chloroforme / diethyl ether to give pure aminoalcohol 29(d) in 73% yield as a white solid, m.p.: 254-256°C. TLC: Rf = 0.2 (ethyl acetate/methylene chloride 1:1).

Following procedure 2(e), the hydrochloride salt 29(d) was prepared in 50% yield after recrystallisation from ethanol / diethyl ether. A white solid, m.p.: 266-268°C. MS: 474 (M^+). Anal. Calc'd for $C_{30}H_{39}ClN_2OS$: C,70.49; H,7.69; N, 5.48; Cl,6.94. Found: C,70.39; H,7.70; N,5.57; Cl,6.82.

EXAMPLE 30

(R,S)-1-(1-Adamantyl)-2-[4-(phenoxazin-10-ylmethyl)piperidin-1-yl]ethanol, fumarate.

a) N-*tert*-Butoxycarbonyl-4-[(10-phenoxazyl)methyl]piperidine.

Compound 30(a) was prepared from phenoxazine (2.91 g, 15.9 mmol) and N-*tert*-Butoxycarbonyl-4-(methanesulphonyloxymethyl)piperidine (4.16 g, 14 mmol) according to the method described in Example 2(c). The

crude product was chromatographed (silica gel, ethyl acetate / hexane 15:85, Rf = 0.3) to afford 30(a) (3.0 g, 54%) as a grey solid, m.p.: 156-158°C.

b) 4-[(10-Phenoxazyl)methyl]piperidine.

Removal of the N-*tert*-butoxycarbonyl protecting group in 30(a) was performed with hydrogen chloride, as described in Example 2(d), to produce 30(b) hydrochloride salt in 77 % yield as a white solid, m.p.: 252-254°C.

The free amine 30(b) was obtained in usual manner in quantitative yield as a white solid, m.p.: 131-133°C.

c)10-[[1-[2-(1-Adamantyl)-2-oxoethyl]-4-piperidinyl]methyl]-phenoxazine.

Amine 30(b) (1.6 g, 5.5 mmol) and 1-(bromoacetyl)adamantane (1.6 g, 6.05 mmol) were converted to aminoketone 30(c) (2 g, 88%), as described in Example 1(c). A colored solid was isolated, m.p.: 166-168°C. TLC: Rf = 0.6 (ethyl acetate/methylene chloride 1:1).

d) (R,S)-1-(1-Adamantyl)-2-[4-(phenoxazin-10-ylmethyl)piperidin-1-yl]-ethanol, fumarate.

Reduction of the aminoketone 30(c) was performed following the method described in Example 1(d). Purification by chromatography (silica gel, ethyl acetate / methylene chloride 3:7) furnished aminoalcohol 30(d) in 87% yield as a solid, m.p.: 180-182°C. TLC: Rf = 0.3 (ethyl acetate / methylene chloride 3:7).

The fumarate salt was crystallized from ethanol in 37% yield following the usual procedure (Example 1(d)). A yellow powder, m.p.: 134.5-135.5°C. MS: 459 (M + 1). Anal. Calc'd for $C_{34}H_{42}N_2O_6$: C,71.06; H,7.37; N,4.87. Found: C,71.38; H,7.87; N,4.96.

Fumarate salt 30(d) contained ca. 5 % of ethanol (basis on ^{1}H-NMR). The salt decomposed slowly when exposed to light.

EXAMPLE 31

(R,S)-1-(1-Adamantyl)-2-[4-(5H-dibenz[b,f]azepin-5-ylmethyl)piperidin-1-yl]ethanol, fumarate.

a) N-*tert*-Butoxycarbonyl-4-[5-(5H-dibenz[b,f]azepinyl)methyl]piperidine.

Compound 31(a) was prepared from 5*H*-dibenz[b,f]azepine (4.25 g, 22 mmol) and N-*tert*-butoxycarbonyl-4-(methanesulfonyloxymethyl) piperidine (6.54 g, 22 mmol) according to the method described in Example 2(c). The crude product was chromatographed (silicagel, methylene chloride / hexane 7:3) to give 31(a) (3.9 g, 45 %) as a viscous oil.

b) 4-[5-(5H-Dibenz[b,f]azepinyl)methyl]piperidine.

Removal of the N-*tert*-butoxycarbonyl protecting group in 31(a) was performed with hydrogen chloride, as described in Example 2(d), to give 31(b) hydrochloride quantitative yield as a gummy solid.
The free amine 31(b) was obtained after usual basic work-up in 79 % yield as a yellow oil.

c)(R,S)-1-(1-Adamantyl)-2-[4-(5H-dibenz[b,f]azepin-5-ylmethyl)piperidin-1-yl]ethanol, fumarate.

Reaction of the (1-adamantyl)ethylene oxide (0.865 g, 4.8 mmol) with piperidine 31(b) (1.4 g, 4.8 mmol) was conducted according to the method described in the Example 11(b), but over 5 hrs. Purification by column chromatography (silica gel, methylene chloride/methanol 9:1) afforded aminoalcohol 31(c) (0.630 g, 28%) as yellow crystals, m.p.: 216-218°C. TLC: Rf = 0.5 (methylene chloride / methanol 9:1).
Following the usual procedure 1(d) the fumarate salt 31(c) was crystallized from ethanol in 66 % as a yellow powder, m.p.: 225-227°C. MS: 468 (M^+). Anal. Calc'd for $C_{36}H_{44}N_2O_5$: C,73.94; H,7.58; N,4.79. Found: C,73.66; H,7.65; N,5.05.

EXAMPLE 32

(R,S)-1-(1-Adamantyl)-2-[4-(10,11-dihydro-5H-dibenz[b,f]azepin-5-ylmethyl)-piperidin-1-yl]ethanol, fumarate.

a) N-*tert*-Butoxycarbonyl-4-[5-(10,11-dihydro-5H-dibenz[b,f]azepinyl) methyl]piperidine.

Compound 32(a) was prepared from 10,11-dihydro-5H-dibenz[b,f]azepine (4.43 g, 22 mmol) and N-*tert*-Butoxycarbonyl-4-(methanesulfonyloxymethyl)piperidine (6 g, 20 mmol) according to the method described in Example 2(c). The crude product was chromatographed (silica gel, methylene chloride / hexane 8:2, Rf = 0.3) to give 32(a) (6.6 g, 76%).

b) 4-[5-(10,11-dihydro-5H-dibenz[b,f]azepinyl)methyl]piperidine.

Removal of the N-*tert*-butoxycarbonyl protecting group in 32(a) was performed with hydrogen chloride, as described in Example 2(d), giving piperidine 32(b) hydrochloride in 79 % yield as a gummy solid. The basic work-up afforded the title free amine 32(b) in 78% yield as a brown oil.

c) (R,S)-1-(1-Adamantyl)-2-[4-(10,11-dihydro-5H-dibenz[b,f]azepin-5-ylmethyl)piperidin-1-yl]ethanol, fumarate.

Reaction of the (1-adamantyl)ethylene oxide (0.980 g, 5 mmol) with piperidine 32(b) (1.46 g, 5 mmol) was conducted according to the method described in the Example 11(b), but over 7 hrs. Purification by column chromatography (silica gel, methylene chloride / methanol 9:1) furnished the title aminoalcohol 32(c) (1.2 g, 51%) as a white solid, m.p.: 172-175°C. TLC: Rf = 0.55 (methylene chloride / methanol 9:1).
According to typical procedure 1(d) the fumarate salt 32(c) was crystallized from ethanol in 61 % yield as a white solid, m.p.: 192-194°C. MS: 471 (M+1). Anal. Calc'd for $C_{36}H_{46}N_2O_5 + H_2O$: C,71.50; H,8.00; N,4.63. Found: C,71.70; H,7.91; N,4.95.

EXAMPLE 33

(R,S)-1-(1-Adamantyl)-2-[4-(5H-phenanthridin-6-oxo-5-ylmethyl)piperidin-1-yl]ethanol, hydrochloride.

a) N-*tert*-Butoxycarbonyl-4-[5*H*-phenanthridin-6-oxo-5-yl)methyl]-piperidine.

Compound 33(a) was prepared from 6-(5H)-phenanthridinone (4.3 g, 22 mmol) and N-*tert*-butoxycarbonyl-4-(methanesulfonyloxymethyl) piperidine (6.0 g, 20 mM) according to the method described in Example 2(c). The crude product was chromatographed (silica gel, ethyl acetate / hexane 3:7, Rf = 0.25) to give 33(a) (4.5 g, 57%) as a white solid, m.p.: 76-79 °C.

b) 4-[5H-Phenanthridin-6-oxo-5-yl)methyl]piperidine.

Removal of the N-*tert*-butoxycarbonyl protecting group in 33(a) was performed with hydrogen chloride, as described in Example 2(d), to give piperidine 33(b) hydrochloride in 93 % yield as a white solid. m.p.: > 250 °C (dec).

The basic work-up produced free amine 33(b) in 89% yield as a white solid.

c) 5-[[1-[2-(1-Adamantyl)-2-oxoethyl]-4-piperidinyl]methyl]-6-(5H)-phenanthridinone.

Following procedure 1(c), amine 33(b) hydrochloride (3.7 g, 11.3 mmol) and 1-(bromoacetyl)adamantane (3.4 g, 13 mmol) were reacted together in acetonitrile (60 ml) containing potassium carbonate (1.7g, 12 mmol). Column chromatography (silica gel, hexane / ethyl acetate / triethylamine 12:8:1) gave aminoketone 33(c) (3.1 g, 59%) as a pale pink solid, m.p.: 98-100 °C.

d)(R,S)-1-(1-Adamantyl)-2-[4-(5H-phenanthridin-6-oxo-5-ylmethyl)-piperidin-1-yl]ethanol, hydrochloride.

Aminoketone 33(c) was reduced following the method described in the Example 1(d). Purification by column chromatography (silica gel, methylene chloride / ethyl acetate / methanol 50:50:1) afforded aminoalcohol 33(d) in 64% yield as white solid, m.p.: 202-203 °C. TLC: Rf = 0.2 (ethyl acetate / methylene chloride 1:1). MS: 305 (M-165). ^{1}H-NMR ($CDCl_3$): 8.54 (dd, 1H); 8.31-8.26 (m, 2H); 7.78-7.76 (m, 1H); 7.73-7.57 (m, 2H); 7.39 (d,1H); 7.31 (t,1H); 4.34 (bd, 2 H); 3.15 (dd, 1H); 3.02 (d, 1H); 2.76 (d, 1H); 2.38-2.19 (m, 3H); 2.04-1.5 (m, 21 H). Anal.Calc'd for $C_{31}H_{38}N_2O_2$: C,79.11; H,8.14; N,5.95. Found: C,79.28; H,8.28; N,5.77.

The title hydrochloride salt was prepared according to example 2(e) in 50 % yield as a white solid, m.p.: 193.5-194.5 °C. Anal. Calc'd for $C_{31}H_{38}N_2O_2$ +

$(HCl)_{1.75}$: C,69.67; H,7.50; N,5.24; Cl,11.61. Found: C,69.67; H,7.57; N,5.23; Cl,11.56.

^{1}H-NMR ($CDCl_3$): 10.55 (bs,1H); 8.45 (dd, 1H); 8.25 (m, 2H); 7.75 (t, 1H); 7.60-7.40 (m, 3H); 7.30 (t,1H); 5.65 (bs,2H); 4.35 (bs, 2 H); 3.75-3.69 (m, 3H); 3.20-3.00 (m, 2H); 3.00-2.60 (m, 2H); 2.35 (bs, 3H); 1.95 (bs, 4H); 1.75-1.40 (m, 12 H).

EXAMPLE 34

(+)-(S)-1-(1-Adamantyl)-2-[4-(5H-phenanthridin-6-oxo-5-ylmethyl)piperidin-1-yl]ethanol, hydrochloride.

Reaction of (+)-S-(1-adamantyl)ethylene oxide (0.500 g, 2.8 mmol) with piperidine 33(b) (0.818 g, 2.8 mmol) was conducted according to the method described in the Example 11(b), but over 72 hrs. Column chromatography (silica gel, methylene chloride / methanol 20:1) gave aminoalcohol 34 (0.980 g, 75%) as a foam. $[a]_D^{20}$ = + 28.8° (c 1.1, $CHCl_3$). TLC: Rf = 0.2 (methylene chloride / methanol 20:1).

^{1}H-NMR ($CDCl_3$): identical to that of racemic aminoalcohol 33(d).

The hydrochloride salt 34 was prepared in 90 % yield according to the usual procedure 2(e). White powder, m.p.: 195-197 °C. $[a]_D^{20}$ = + 14.2 ° (c 1, $CHCl_3$). ^{1}H-NMR ($CDCl_3$): identical to that of hydrochloride salt 33(d).

Anal. Calc'd for $C_{31}H_{38}N_2O_2$ + HCl + H_2O: C,70.90; H,7.87; N,5.33; Cl,6.75. Found: C,70.59; H,7.82; N,5.26; Cl,6.81.

EXAMPLE 35

(-)-(R)-1-(1-Adamantyl)-2-[4-(5H-phenanthridin-6-oxo-5-ylmethyl)piperidin-1-yl]ethanol, hydrochloride.

Reaction of the (-)-R-(1-adamantyl)ethylene oxide (0.500 g, 2.8 mmol) with piperidine 33(b) (0.818 g, 2.8 mmol) was conducted according to the method described in Example 11(b), but over 35 hrs. Crude product was subjected to column chromatography (silica gel, methylene chloride / methanol

20:1)to give aminoalcohol 35 (0.980 g, 74%) as a white powder, m.p.: 101-103°C. $[a]_D^{20}$ = - 30.5 ° (c 1, $CHCl_3$). TLC: Rf = 0.2 (methylene chloride / methanol 20:1). ^{1}H-NMR ($CDCl_3$): identical to that of aminoalcohol 33(d).

The hydrochloride salt 35 was prepared in 90 % yield according to the usual method 2(e). White powder, m p : 269-271°C. $[a]_D^{20}$ = - 18.5 ° (c 1, $CHCl_3$). ^{1}H-NMR ($CDCl_3$): identical to that of hydrochloride 33(d).

Anal. Calc'd for $C_{31}H_{38}N_2O_2$ + HCl + 1.3 H_2O: C,70.20; H,7.79; N,5.28; Cl,6.70. Found: C,70.20; H,7.66; N,5.19; Cl,6.69.

EXAMPLE 36

(R,S)-1-(1-Adamantyl)-2-[4-(10,11-dihydrodibenz[b,f][1,4]oxazepin-11-oxo-10-ylmethyl)piperidin-1-yl]ethanol, hemitartrate.

a) N-*tert*-Butoxycarbonyl-4-[(10,11-dihydrodibenz[b,f][1,4]oxazepin-11-oxo-10-yl)methyl]piperidine.

Compound 36(a) was prepared from 10,11-dihydrodibenz[b,f][1,4]-oxazepin-11-one (4.3 g, 22 mmol) and N-*tert*-Butoxycarbonyl-4-(methanesulfonyloxymethyl)piperidine (6.0 g, 20 mmol) according to the method described in Example 2(c). The crude product was chromatographed (silicagel, ethyl acetate / methylene chloride 1:9) affording 36(a) (6 g, 74 %) as an orange oil. TLC: Rf = 0.3 (ethyl acetate /methylene chloride 1:9).

b) 4-[(10,11-Dihydrodibenz[b,f][1,4]oxazepin-11-oxo-10-yl)methyl] piperidine.

Removal of the N-*tert*-butoxycarbonyl protecting group in 36(a) was performed with hydrogen chloride, as described in Example 2(d), to give piperidine 36(b) hydrochloride in 53% yield as a white powder, m.p.: > 250 °C. The free amine 36(b) was obtained, after usual basic work-up, in 90 % yield as a foam.

c)10-[[1-[2-(1-Adamantyl)-2-oxoethyl]-4-piperidinyl]methyl]-10,11-dihydrodibenz[b,f][1,4]oxazepin-11-one.

Piperidine 36(b) (2.7 g, 8.8 mmol) and 1-(bromoacetyl) adamantane (2.83 g, 11 mmol) were converted to aminoketone 36(c) (3 g, 70%), as described in Example 1(c). The pure product was obtained after chromatography (silica gel, hexane / ethyl acetate 1:1) as a pale yellow oil. TLC: Rf = 0.2 (hexane / ethyl acetate 1:1).

d) (R,S)-1-(1-Adamantyl)-2-[4-(10,11-dihydrodibenz[b,f][1,4]oxazepin-11-oxo-10-ylmethyl)piperidin-1-yl]ethanol, hemitartrate.

Aminoketone 36(c) (3 g, 6 mmol) was reduced following the procedure 1(d). Column chromatography (silica gel, methylene chloride / methanol 95:5) gave aminoalcohol (1.7 g, 58%) as a foam. TLC: Rf = 0.5 (methylene chloride / methanol 9:1).

The hemitartrate salt 36(d) was crystallized, in a usual way, from ethanol in 69% yield as a white solid, m.p.: 221.1-223.4°C. MS: 321 (M-165). Anal. Calc'd for $C_{33}H_{41}N_2O_6$ + 1.25 H_2O: C,67.78; H,7.45; N,4.81. Found: C,67.70; H,7.29; N,4.81.

EXAMPLE 37

(R,S)-1-(1-Adamantyl)-2-[4-(10,11-dihydrodibenzo[b,e][1,4]diazepin-11-oxo-10-ylmethyl)piperidin-1-yl]ethanol, hydrochloride.

a) N-*tert*-Butoxycarbonyl-4-[(10,11-dihydrodibenzo[b,f][1,4]diazepin-11-oxo-10-yl)methyl]piperidine.

Compound 37(a) was prepared from 10,11-dihydrodibenzo[b,e][1,4]diazepin-11-one (4.6 g, 22 mmol) and N-*tert*-Butoxycarbonyl-4-(methanesulfonyloxymethyl)piperidine (6.0 g, 20 mmol) according to the method described in Example 2(c). The crude product was chromatographed (silicagel, ethyl acetate / methylene chloride 1:9) yielding 37(a) (3.2 g, 39 %) as an oil. TLC: Rf = 0.4 (diethyl ether / methylene chloride 2:8).

The starting 10,11-dihydrodibenzo[b,e][1,4]diazepin-11-one was prepared according to Monro A.M. *et al.*[*J. Med. Chem.* 1963, 255-261].

b) 4-[(10,11-Dihydrodibenzo[b,e][1,4]diazepin-11-oxo-10-yl)methyl]piperidine.

Removal of the *tert*-butyloxycarbonyl protecting group in 37(a) was performed with hydrogen chloride, as described in Example 2(d), to give piperidine 37(b) hydrochloride in quantitative yield as a powder, m.p.: > 250 °C. The free amine 37(b) was obtained in a usual way, in quantitative yield as a foam.

c) (R,S)-1-(1-Adamantyl)-2-[4-(10,11-dihydrodibenzo[b,e][1,4]diazepin-11-oxo-10-ylmethyl)piperidin-1-yl]ethanol, hydrochloride.

Reaction of the (1-adamantyl)ethylene oxide (0.500 g, 2.8 mmol) with piperidine 37(b) (0.860 g, 5 mmol) was conducted according to the method described in Example 11(b), but over 48 hrs. Purification by column chromatography (silica gel, methylene chloride / methanol 20:1) afforded aminoalcohol 37(c) (1.04 g, 77%) as a white foam. TLC: Rf = 0.44 (methylene chloride / methanol 9:1).

The hydrochloride salt 37(c) was prepared, following general procedure 2(e), in 69% yield as a white solid, m.p.: 196-198°C. MS: 320 (M-165). Anal. Calc'd for $C_{31}H_{39}N_3O_2$ + HCl + 0.5 H_2O: C,70.06; H,7.72; N,7.90;Cl,6.68. Found : C,70.07; H,7.94; N,7.76;Cl,6.77.

EXAMPLE 38

(R,S)-1-(1-Adamantyl)-2-[4-(10,11-dihydrodibenzo[b,f][1,4]thiazepin-11-oxo-10-ylmethyl)piperidin-1-yl]ethanol, fumarate.

a) N-*tert*-Butoxycarbonyl-4-[(10,11-dihydrodibenzo[b,f][1,4]thiazepin-11-oxo-11-yl)methyl]piperidine.

Compound 38(a) was prepared from 10,11-dihydrodibenzo[b,f][1,4]thiazepin-11-one (2.27 g, 10 mmol) and N-*tert*-Butoxycarbonyl-4-(methanesulfonyloxymethyl)piperidine (2.93 g, 10 mmol) according to the method described in Example 2(c). The crude product was subjected to column chromatography (silica gel, ethyl acetate / hexane 3:7, Rf = 0.25) to give 38(a) (2.92 g, 69%) as a white solid.

The starting 10,11-dihydrodibenzo[b,f][1,4]thiazepin-11-one was prepared according to JAQUES *et al.* [*Helv. Chim. Acta* 1959, 1265].

b) 4-[(10,11-Dihydrodibenzo[b,f][1,4]thiazepin-11-oxo-10-yl)methyl] piperidine.

Removal of the *tert*-butyloxycarbonyl protecting group in 38(a) was performed with hydrogen chloride, as described in Example 2(d), to give piperidine 38(b) hydrochloride in 84 % yield as a white powder, m.p.: 248.2-250.2 °C.

The usual basic work-up produced free amine 38(b) in quantitative yield as an oil.

c) (R,S)-1-(1-Adamantyl)-2-[4-(10,11-dihydrodibenzo[b,f][1,4]thiazepin-11-oxo-10-ylmethyl)piperidin-1-yl]ethanol, fumarate.

Reaction of the (1-Adamantyl)ethylene oxide (0.470 g, 2.6 mmol) with piperidine 38(b) (0.860 g, 2.6 mmol) was conducted according to the method described in Example 11(b), but over 72 hrs. Column chromatography (silica gel, methylene chloride / methanol 9:1) gave aminoalcohol 38(c) (0.800 g, 61 %) as a white solid, m.p.: 217-220°C. TLC: Rf = 0.2 (methylene chloride / methanol 20:1).

The fumarate salt 38(c) was crystallized from ethanol, following usual procedure, in 72 % yield as a white solid, m.p.: 207-209°C. MS: 337 (M-165). Anal. Calc'd for $C_{35}H_{42}N_2O_6S$: C,67.94; H,6.84; N,4.53. Found: C,67.73; H,6.85; N,4.43.

EXAMPLE 39

(R,S)-1-(1-Adamantyl)-2-[4-(5,6,11,12-tetrahydrodibenz[b,f]azocin-6-oxo-5-ylmethyl)piperidin-1-yl]ethanol, maleate.

a) N-*tert*-Butoxycarbonyl-4-[(5,6,11,12-tetrahydrodibenz[b,f]azocin-6-oxo-5-yl)methyl]piperidine.

Compound 39(a) was prepared from 5,6,11,12-tetrahydrodibenzo[b,f]azocin-6-one (5 g, 22 mmol) and N-*tert*-Butoxycarbonyl-4-(methanesulfonyloxymethyl)piperidine (6.0 g, 20 mmol) according to the method described in Example 2(c). The crude product was chromatographed (silica gel, ethyl acetate / methylene chloride 1:9) to produce 39(a) (7.8 g, 90%) as a white solid, m.p.: 122-124°C. TLC: Rf = 0.7 (ethyl acetate / methylene chloride 1:9).

b) 4-[(5,6,11,12-tetrahydrodibenz[b,f]azocin-6-oxo-5-yl)methyl] piperidine.

Removal of the N-*tert*-butoxycarbonyl protecting group in 39(a) was performed with hydrogen chloride, as described in Example 2(d), to give piperidine 39(b) hydrochloride as a white powdered solid, m.p.: 154-156°C. The usual basic work-up afforded free amine 39(b) (4g, 67%) as a white solid, m.p.: 114-116°C.

c) 5-[[1-[2-(1-Adamantyl)-2-oxoethyl]-4-piperidinyl]methyl]-5,6,11,12-tetrahydrodibenz[b,f]azocin-6-one.

The piperidine 39(b) (3.9 g, 11.7 mmol) and 1-(bromoacetyl) adamantane (3.6 g, 14 mmol) were converted to the aminoketone 39(c) (3.1 g, 53%) following the procedure 1(c). The pure product was obtained after column chromatography (silica gel, methylene chloride / ethyl acetate 1:1) as a pale yellow oil. TLC: Rf = 0.15 (hexane / ethyl acetate 1:1).

d) (R,S)-1-(1-Adamantyl)-2-[4-(5,6,11,12-tetrahydrodibenz[b,f]azocin-6-oxo-5-ylmethyl)piperidin-1-yl]ethanol, maleate.

Aminoketone 39(c) (3 g, 6 mmol) was reduced according to procedure 1(d). Purification by column chromatography (silica gel, methanol/methylene chloride 5:95) gave aminoalcohol 39(d) in quantitative yield as a white solid, m.p.: 162.5-164.4 °C. TLC: Rf = 0.5 (methylene chloride / methanol 9:1).

The maleate salt 39(d) was crystallized from ethanol / diethyl ether, in a usual way, in 81% yield as a white solid, m.p.: 224.5-225.5°C. MS: 333 (M-165). Anal. Calc'd for $C_{37}H_{46}N_2O_6$ + 0.25 H_2O: C,71.84; H,7.54; N,4.56. Found: C,71.80; H,7.65; N,4.68.

EXAMPLE 40

(R,S)-1-(1-Adamantyl)-2-[4-(5,6,11,12-tetrahydrodibenz[b,f]azocin-5-ylmethyl)piperidin-1-yl]ethanol, fumarate.

a) N-*tert*-Butoxycarbonyl-4-[(5,6,11,12-tetrahydrodibenz[b,f]azocin-5-yl)methyl]piperidine.

Compound 40(a) was prepared from 5,6,11,12-tetrahydrodibenzo[b,f]azocine (3.81 g, 18 mmol) and N-*tert*-butoxycarbonyl-4-(methanesulfonyloxymethyl)piperidine (5.41 g, 20 mmol) according to the method described in Example 2(c). Column chromatography (silica gel, ethyl acetate / methylene chloride 1:9) gave 40(a) in 80 % yield.

b) 4-[(5,6,11,12-tetrahydrodibenz[b,f]azocin-5-yl)methyl]piperidine.

Removal of the *tert*-butoxycarbonyl protecting group in 40(a) was performed with hydrogen chloride, as described in Example 2(d), to give piperidine 40(b) hydrochloride as an oil. The usual basic work-up furnished free amine 40(b) as a foam in 80 % overall yield.

c) 5-[[1-[2-(1-Adamantyl)-2-oxoethyl]-4-piperidinyl]methyl]-5,6,11,12-tetrahydrodibenz[b,f]azocine.

The piperidine 40(b) (3.49 g, 11.4 mmol) was reacted with 1-(bromoacetyl)adamantane (3.2 g, 12.5 mmol) following the procedure 1(c). Purification by column chromatography (silica gel, methylene chloride / methanol 97:3) afforded aminoketone 40(c) (1.4 g, 25%) as an orange oil. TLC: Rf = 0.3 (methylene chloride / methanol 97:3).

d)(R,S)-1-(1-Adamantyl)-2-[4-(5,6,11,12-tetrahydrodibenz[b,f]azocin-5-ylmethyl)piperidin-1-yl]ethanol, fumarate.

Reduction of the aminoketone 40(c) (1.36 g, 2.8 mmol), according to the method described in Example 1(d), followed by column chromatography (silica gel, methylene chloride / ethyl acetate 5:1) gave aminoalcohol (0.57 g, 42%) as a white solid, m.p.: 153.7-154.8°C. TLC: Rf = 0.6 (methylene chloride/methanol 9:1).

Following the usual way, fumarate salt 40(d) was crystallized from ethanol in 52 % yield as a white solid, m.p.: 182.0-183.4°C. MS: 319 (M-165). Anal. Calc'd for $C_{37}H_{48}N_2O_5 + H_2O$: C,71.82; H,8.14; N,4.53. Found: C,71.80; H,8.20; N, 4.46.

EXAMPLE 41

(R,S)-1-(1-Adamantyl)-2-[4-(6H-dibenzo[c,e][1,2]thiazin-6-ylmethyl)piperidin-1-yl]ethanol S,S-dioxide, hydrochloride.

a)N-*tert*-Butoxycarbonyl-4-[6-(6H-dibenzo[c,e][1,2]thiazin)methyl]-piperidine S,S-dioxide.

Compound 41(a) was prepared from 6-(6H-dibenzo[c,e][1,2]thiazine 5,5-dioxide (4.62 g, 20 mmol) and N-*tert*-Butoxycarbonyl-4-(methanesulfonyloxymethyl)piperidine (6.0 g, 20 mmol) according to the method described in Example 2(c). Column chromatography (silicagel, ethyl acetate / hexane 3:7, TLC: Rf = 0.2) furnished 41(a) (5.21 g, 61%) as a white solid.

6-(6H-Dibenzo[c,e][1,2]thiazine 5,5-dioxide was prepared according to Ullmann F., Grob C., *Chem. Ber.*, 1910, *43*, 2694.

b) 4-[6-(6H-Dibenzo[c,e][1,2]thiazin)methyl]piperidine S,S-dioxide.

Removal of the N-*tert*-butoxycarbonyl protecting group in 41(a) was performed with hydrogen chloride, as described in Example 2(d), to give piperidine 41(b) hydrochloride in quantitative yield as a white solid, m.p.: 128-130°C.

After the usual basic work-up, the free amine 41(b) was isolated in 92% yield as a solidified foam.

c) 6-[[1-[2-(1-Adamantyl)-2-oxoethyl]-4-piperidinyl]methyl]-6H-dibenzo-[c,e][1,2]thiazine 5,5-dioxide.

Reaction of amine 41(b) (2.4 g, 7.4 mmol) with 1-(bromoacetyl)adamantane (2.1 g, 8.1 mmol) was performed as described in Example 1(c). Column chromatography (silicagel, methylene chloride / ethyl acetate 1:1, TLC: Rf = 0.27) gave aminoketone 41(c) (2.7 g, 72%) as a white solidified foam.

d) (R,S)-1-(1-Adamantyl)-2-[4-(6H-dibenzo[c,e][1,2]thiazin-6-ylmethyl)piperidin-1-yl]ethanol S,S-dioxide, hydrochloride.

Reduction of aminoketone 41(c) (2.6 g, 5.1 mmol), according to the method described in Example 1(d), followed by column chromatography (silicagel, methylene chloride / ethyl acetate 1:1) gave aminoalcohol 41(d) (1.8 g, 70%) as a solidified foam. TLC: Rf = 0.3 (ethyl acetate / methylene chloride 1:1). ^{1}H-NMR ($CDCl_3$): 8.00 (m, 3H); 7.70 (t, 1H); 7.55 (t,1H); 7.45 (d, 1H); 7.35 (m,2H); 3.85 (d, 2 H); 3.15 (dd, 1H); 3.00 (bd, 1H); 2.7 (bd, 1H); 2.4-1.2 (m, 24 H).

Following procedure 2(e), the title hydrochloride salt 41(d) was prepared in

62% yield as a white solid, m.p.: 242-244°C. Anal. Calc'd for $C_{30}H_{39}ClN_2O_3S$: C,66.34; H,7.24; N,5.16; Cl,6.53. Found: C,66.21; H,7.24; N,5.10; Cl,6.69. MS: 341 (M-165). ^{1}H-NMR ($CDCl_3$): 10.3 (bs, 1H); 8.00 (m, 3H); 7.75 (m, 1H); 7.60-7.30 (m, 4H); 4.00 (d, 1 H); 3.65 (m, 4H); 3.30 (bm, 1H); 3.0 (bm, 3H); 2.65 (bm, 2H); 2.2-1.4 (m, 19 H).

EXAMPLE 42

(+)-(S)-1-(1-Adamantyl)-2-[4-(6H-dibenzo[c,e][1,2]thiazin-6-ylmethyl)piperidin-1-yl]ethanol S,S-dioxide, hydrochloride.

Reaction of (+)-(S)-(1-adamantyl)ethylene oxide (0.500 g, 2.8 mmol) with piperidine 41(b) (0.923 g, 2.8 mmol) was conducted according to the method described in Example 11(b), but over 72 hrs. Column chromatography (silicagel, methanol / methylene chloride 20:1) furnished aminoalcohol 42 (1.13 g, 80%) as a solidified foam. $[a]_D^{20}$ = + 22.8° (c 1.1 , $CHCl_3$). TLC: Rf = 0.3 (methanol / methylene chloride 1:20). ^{1}H-NMR ($CDCl_3$): identical to that of the racemic aminoalcohol 41(d).

The hydrochloride salt 42 was prepared, according to the usual method 2(e), as a white solid, m.p.: 209.3-210.6°C. $[a]_D^{20}$ = + 12.5° (c 0.7, $CHCl_3$). ^{1}H-NMR ($CDCl_3$): identical to that of the hydrochloride 41(d).

Anal. Calc'd for $C_{30}H_{39}ClN_2O_3S$: C,66.34; H,7.24; N,5.16; Cl,6.53. Found: C,66.17; H,7.25; N,5.12; Cl,6.50.

EXAMPLE 43

(-)-(R)-1-(1-Adamantyl)-2-[4-(6H-dibenzo[c,e][1,2]thiazin-6-ylmethyl)piperidin-1-yl]ethanol S,S-dioxide, hydrochloride.

Reaction of the (-)-(R)-(1-adamantyl)ethylene oxide (0.500 g, 2.8 mmol) with piperidine 41(b) (0.923 g, 2.8 mmol) was performed according to the procedure described in Example 11(b), but over 60 hrs. Purification by column chromatography (silicagel, methanol / methylene chloride 20:1) afforded aminoalcohol 43 (0.970 g, 68%) as a solidified foam. $[a]_D^{20}$ = - 27.4° (c 1,

$CHCl_3$). TLC: Rf = 0.3 (methanol / methylene chloride 1:20). ^{1}H-NMR ($CDCl_3$): identical to that of the aminoalcohol 41(d).

The hydrochloride salt 43 was prepared, according to the usual method 2(e), as a white hygroscopic solid, m.p. = 209-210 °C. $[a]_D^{20}$ = - 15.3° (c 1.1 , $CHCl_3$). ^{1}H-NMR ($CDCl_3$): identical to that of the hydrochloride 41(d).

Anal. Calc'd for $C_{30}H_{38}N_2O_3S$ + HCl + 0.3 H_2O : C,65.57; H,7.21; N,5.10; Cl,6.47. Found: C,65.64; H,7.29; N,5.11; Cl,6.44.

EXAMPLE 44

(+)-(S)-6-[1-[2-(1-Adamantyl)-2-methoxyethyl]piperidin-4-ylmethyl]-6H-dibenzo[c,e][1,2]thiazine 5,5-dioxide, hydrochloride.

The O-methylation of the (+)-S-aminoalcohol 42 (0.450 g, 0.89 mmol) was performed as described in Example 21. After column chromatography (silica gel, ethyl acetate / methylene chloride 2:3, TLC: Rf = 0.2), the title methyl ether 44 (0.200 g, 44%) was obtained as a white solidified foam . ^{1}H-NMR ($CDCl_3$): 8.00 (m, 3H); 7.70 (t, 1H); 7.55 (t,1H); 7.45 (d, 1H); 7.35 (m,2H); 3.85 (d, 2 H); 3.4 (s,3H); 2.7-2.2 (m, 5H); 2.0-1.2 (m, 22 H).

The hydrochloride salt 44 was prepared according to the usual method 2(e) as a white foam. $[a]_D^{20}$ = + 12.1° (c 1, $CHCl_3$). MS 341 (M-179).

Anal. Calc'd for $C_{31}H_{40}N_2O_3S$ + HCl + 1.3 H_2O: C,64.03; H,7.51; N,4.82; Cl,6.11. Found: C,64.06; H,7.59; N,4.54; Cl,6.12.

EXAMPLE 45

(-)-(R)-6-[1-[2-(1-Adamantyl)-2-methoxyethyl]piperidin-4-ylmethyl]-6H-dibenzo[c,e][1,2]thiazine 5,5-dioxide, hydrochloride.

The O-methylation of (-)-R-aminoalcohol 43 (0.450 g, 0.89 mmol) was performed as described in Example 21. Column chromatography (silicagel, ethyl acetate / methylene chloride 2:3, TLC: Rf = 0.2) afforded the title methyl ether 45 (0.170 g, 37%) as a white foam. ^{1}H-NMR ($CDCl_3$): identical to that of methyl ether 44.

The hydrochloride salt 45 was prepared according to the usual method 2(e) as a foam. $[a]_D^{20}$ = - 15.0° (c 1 , $CHCl_3$).
Anal. Calc'd for $C_{31}H_{40}N_2O_3S$ + HCl + 1.3 H_2O: C,64.03; H,7.51; N,4.82; Cl,6.11. Found: C,63.85; H,7.48; N,4.74; Cl,6.31.

EXAMPLE 46

(R,S)-1-(1-Adamantyl)-2-[4-(8-fluoro-6H-dibenzo[c,e][1,2]thiazin-6-ylmethyl)-piperidin-1-yl]ethanol S,S-dioxide, fumarate.

a) 8-Fluoro-6H-dibenzo[c,e][1,2]-thiazine 5,5-dioxide.

To a stirred solution of 3-fluoroaniline (11.11 g, 100 mmol) in ethyl acetate (40 ml) and pyridine (8.2 ml, 100 mmol) was slowly added dropwise a solution of 2-nitrobenzenesulfonyl chloride (22.16 g, 100 mmol) in ethyl acetate (60 ml). The mixture was stirred for 5 hours at room temperature and then heated at 80°C for 15 min. After cooling, the reaction mixture was filtered and the solid washed with ethyl acetate. The organic solution was washed with 2N hydrochloric acid, then dried and evaporated. The residue was purified by filtration through a silica pad (hexane / ethyl acetate 1:1). Evaporation of the solvent and recrystallization from toluene-hexane gave 2-nitrobenzenesulfon-3'-fluoroanilide (23.5 g, 79 %) as pinky crystals, mp : 130.2-132 °C.
To a solution of the above o-nitrobenzenesulfonamide (22.2 g, 75 mmol) in ethyl acetate (200 ml) was added tin (II) chloride dihydrate (84.5 g, 375 mmol) and resulted mixture heated at 80°C for 2 hrs. After cooling, the reaction mixture was poured into water (400 ml), the solution was basified with 2N sodium hydroxyde and extracted with ethyl acetate. Combined organic extracts were dried and evaporated to give a waxy solid of 2-aminobenzenesulfon-3'-fluoroanilide (19.97 g, 100%) which was used in the next step without further purification.
To a solution of the above o-aminobenzenesulfonamide (10.65 g, 40 mmol) in acetic acid (30 ml) was added concentrated hydrochloric acid (60 ml). Then, on cooling below 10 °C, a solution of sodium nitrite (3.04 g, 44 mmol) in water (15 ml) was slowly added dropwise. The reaction mixture was vigorously stirred for 45 min., then diluted with water (50 ml), filtered and the filtrate heated at 100°C for 45 min. After cooling, the mixture was extracted with ethyl acetate, combined organic extracts were washed with water, dried and evaporated. Residual solid

was purified by filtration through a silica pad (hexane / ethyl acetate 1:2) and recrystallized from ethanol / hexane yielding fluoro-sultam 46(a) (1.74 g, 18%) as an orange crystalline solid, m.p.: 205.8-206.8 °C. TLC: Rf = 0.43 (hexane / ethyl acetate 1:1).

^{1}H-NMR (DMSO-D$_6$): 11.67 (bs, 1H), 8.30 (dd, 1H-C$_{10}$); 8.22 (dd, 1H-C$_4$); 7.96 (dd,1H-C$_1$); 7.81 (dt, 1H-C$_3$); 7.65 (dt,1H-C$_2$); 7.18 (dt, 1H-C$_9$); 7.00 (dd, 1H-C$_7$). The proton signals were assigned with the aid of H,H-COSY experiment.

b) 4-(8-Fluoro-6H-dibenzo[c,e][1,2]thiazin-6-ylmethyl)piperidine S,S-dioxide.

Starting from fluoro-sultam 46(a) and N-*tert*-butoxycarbonyl-4-(metanesulfonyloxymethyl)piperidine and following the usual procedures described in Examples 2(c) and 2(d) the piperidine 46(b) hydrochloride was synthesized in 51% yield as a pinky hygroscopic solid.
Typicall basic work-up afforded free amine 46(b) as an oil.

c) (R,S)-1-(1-Adamantyl)-2-[4-(8-fluoro-6H-dibenzo[c,e][1,2]thiazin-6-ylmethyl)-piperidin-1-yl]ethanol S,S-dioxide, fumarate.

Reaction of the (1-adamantyl)ethylene oxide (0.890 g, 5 mmol) with piperidine 46(b) (1.75 g, 5 mmol) was conducted according to the method described in Example 11(b), but over 12 hrs. Column chromatography (silicagel, methylene chloride / methanol 9:1, TLC: Rf = 0.54) furnished the title aminoalcohol 46(c) (0.75 g, 28%) as a white solid, m.p.: 247.2-247.8 °C.
The fumarate salt 46(c) was crystallized from ethanol / diethyl ether, according to the usual procedure, as a white hygroscopic solid, m.p.: 138.7-140.2 °C. MS: 359 (M-165). Anal. Calc'd for $C_{34}H_{41}FN_2O_7S$ + 1/2 H_2O: C,62.77; H,6.46; N,4.31. Found: C,62.65; H,6.65; N,4.31.

EXAMPLE 47

(R,S)-1-(1-Adamantyl)-2-[4-(9-fluoro-6H-dibenzo[c,e][1,2]thiazin-6-ylmethyl)-piperidin-1-yl]ethanol S,S-dioxide, hydrochloride.

a) 9-Fluoro-6H-dibenzo[c,e][1,2]thiazine 5,5-dioxide.

The title fluoro-sultam 47(a) was synthesized from 4-fluoroaniline following the sequence of reactions described in Example 46(a). Reaction with

2-nitrobenzenesulfonyl chloride gave 2-nitrobenzenesulfon-4'-fluoroanilide in 66% yield as a solid, m.p.: 104.7-105.9°C. Next, reduction of the nitro group provided crude 2-aminobenzenesulfon-4'-fluoroanilide in 88% yield. Finally, decomposition of diazonium salt and recrystallization from ethyl acetate / hexane afforded fluoro-sultam 47(a) in 25% yield as an orange crystalline solid, m.p.: 214.7-215.7°C. TLC: Rf = 0.55 (ethyl acetate / hexane 1:1).

b) 4-(9-Fluoro-6H-dibenzo[c,e][1,2]thiazin-6-ylmethyl)piperidine S,S-dioxide.

Starting from fluoro-sultam 47(a) and N-*tert*-butoxycarbonyl-4-(methanesulfonyloxymethyl)piperidine and following the usual procedures described in Examples 2(c) and 2(d), the piperidine 47(b) hydrochloride was obtained in 70 % yield as a white solid, m.p.: 186-190°C.
Typicall basic work-up provided free amine 47(b) as an oil.

c) (R,S)-1-(1-Adamantyl)-2-[4-(9-fluoro-6H-dibenzo[c,e][1,2]thiazin-6-ylmethyl)-piperidin-1-yl]ethanol S,S-dioxide, hydrochloride.

Reaction of (1-adamantyl)ethylene oxide (1.33 g, 7.5 mmol) with piperidine 47(b) (2.6 g, 7.5 mmol) was conducted following the method described in Example 11(b), but over 18 hrs. Purification by column chromatography (silica gel, methylene chloride / methanol 9:1, TLC: Rf = 0.56) furnished aminoalcohol 47(c) (1.4 g, 35%) as a white solid, m.p. :198-199°C. The hydrochloride salt 47(c) was prepared according to the usual procedure described in Example 2(e) as a white solid, m.p.: 214.5-216.5°C. MS: 359 (M-165). Anal. Calc'd for $C_{30}H_{38}ClFN_2O_3S$: C,64.21; H,6.83; N,4.99; Cl,6.32. Found: C,63.91; H,6.87; N,4.97;Cl,6.36.

EXAMPLE 48

(R,S)-1-(1-Adamantyl)-2-[4-(7-fluoro-6H-dibenzo[c,e][1,2]thiazin-6-ylmethyl)-piperidin-1-yl]ethanol S,S-dioxide, hydrochloride.

a)7-Fluoro-6H-dibenzo[c,e][1,2]thiazine 5,5-dioxide.

The title fluoro-sultam 48(a) was prepared from 2-fluoroaniline following the sequence of reactions described in Example 46(a). Reaction with 2-nitrobenzenesulfonyl chloride gave 2-nitrobenzenesulfon-2'-fluoroanilide in 54% yield as a pink solid, m.p.: 110.3-112.6 °C. Next, reduction of the nitro group provided crude 2-aminobenzenesulfon-2'-fluoroanilide in 88% yield. Finally, decomposition of diazonium salt and recrystallization from ethyl acetate / hexane (3:7) afforded fluorosultam 48(a) in 26% as an orange solid, m.p.: 206.0-210.3°C. TLC: Rf = 0.25 (ethyl acetate / hexane 3:7).

b) 4-(7-Fluoro-6H-dibenzo[c,e][1,2]thiazin-6-ylmethyl)piperidine S,S-dioxide.

Starting from fluoro-sultam 48(a) and N-*tert*-butoxycarbonyl-4-(methanesulfonyloxymethyl)piperidine and following procedures described in Examples 2(c) and 2(d) , the piperidine 48(b) hydrochloride was prepared in 72 % yield as a white solid. m.p.: > 250 °C.
Usual basic work-up gave free amine 48(b) in quantitative yield as an oil.

c) (R,S)-1-(1-Adamantyl)-2-[4-(7-fluoro-6H-dibenzo[c,e][1,2]thiazin-6-ylmethyl)piperidin-1-yl]ethanol S,S-dioxide, hydrochloride.

Reaction of the (1-adamantyl)ethylene oxide (0.566 g, 3.2 mmol) piperidine 48(b) (1.10 g, 3.2 mmol) was performed according to the method described in the Example 11(b), but over 67 hrs. Column chromatography (silica gel, methylene chloride / methanol 20:1, TLC: Rf = 0.32) provided aminoalcohol 48(c) (1.34 g, 80%) as a solidified foam.
The hydrochloride salt 48(c) was prepared according to the procedure described in Example 2(e) as a white solid, m.p.: 228.2-230.1°C. MS: 359 (M-165). Anal. Calc'd for $C_{30}H_{38}ClFN_2O_3S$: C,64.21; H,6.83; N,4.99; Cl,6.32. Found: C,63.96; H,6.94; N,4.83; Cl,6.40.

EXAMPLE 49

(R,S)-1-(1-Adamantyl)-2-[4-(8-chloro-6H-dibenzo[c,e][1,2]thiazin-6-ylmethyl)-piperidin-1-yl]ethanol S,S-dioxide, hydrochloride.

a) 8-Chloro-6H-dibenzo[c,e][1,2]thiazine 5,5-dioxide.

The title chloro-sultam 49(a) was synthesized from 3-chloroaniline

following the sequence of reactions described in Example 46(a). Reaction with 2-nitrobenzenesulfonyl chloride gave 2-nitrobenzenesulfon-3'-chloroanilide in 52% yield as a yellow powder, m.p.: 122-123°C. Next, reduction of the nitro group provided crude 2-aminobenzenesulphon-3'-chloroanilide in 67% yield. Finally, decomposition of diazonium salt and recrystallization from methylene chloride / hexane afforded chloro-sultam 49(a) in 27% yield as a white crystalline solid, m.p.: 219-220 °C. TLC: Rf = 0.51 (ethyl acetate / hexane 1:1). ^{1}H-NMR (DMSO-D6) : 11.6 (bs, 1H), 8.13 (dd, 1H-C4); 8.12 (dd, 1H-C10); 7.95 (dd,1H-C1); 7.82 (dt, 1H-C3); 7.68 (dt,1H-C2); 7.35 (dd, 1H-C9); 7.21 (d, 1H-C7).

b) 4-(8-Chloro-6H-dibenzo[c,e][1,2]thiazin-6-ylmethyl)piperidine S,S-dioxide.

Starting from chloro-sultam 49(a) and N-*tert*-butoxycarbonyl-4-(methanesulfonyloxymethyl)piperidine and following usual process described in the Examples 2(c) and 2(d), the piperidine 49(b) hydrochloride was prepared in 63 % yield as a white solid, m.p.: > 250 °C.
Usual basic work-up provided free amine 49(b) as an oil.

c) (R,S)-1-(1-adamantyl)-2-[4-(8-chloro-6H-dibenzo[c,e][1,2]thiazin-6-ylmethyl)-piperidin-1-yl]-ethanol S,S-dioxide.

Reaction of (1-adamantyl)ethylene oxide (0.5 g, 2.8 mmol) with piperidine 49(b) (1.016 g, 2.8 mmol) was conducted according to the method described in the Example 11(b), but over 68 hrs. Purification by column chromatography (silica gel, methylene chloride / methanol 20:1, TLC: Rf = 0.39) furnished the title aminoalcohol 49(c) (0.910 g, 60 %) as a white solidified foam.
The hydrochloride salt 49(c) was prepared according to the procedure described in Example 2(d), as a white solid, m.p.: 176-177°C. MS: 375 (M-165). Anal. Calc'd for $C_{30}H_{38}Cl_2N_2O_3S$ + 2/3 H_2O: C,61.01; H,6.66; N,4.74; Cl,12.03. Found: C,61.03; H,6.98; N,4.62; Cl,12.16.

EXAMPLE 50

(R,S)-1-(1-Adamantyl)-2-[4-(8-methoxy-6H-dibenzo[c,e][1,2]thiazin-6-ylmethyl)piperidin-1-yl]ethanol S,S-dioxide, hydrochloride.

a) 8-Methoxy-6H-dibenzo[c,e][1,2]thiazine 5,5-dioxide.

The title methoxy-sultam 50(a) was prepared from 3-methoxy aniline following the sequence of reactions described in Example 46(a). Reaction with 2-nitrobenzenesulfonyl chloride gave 2-nitrobenzenesulfon-3'-methoxyanilide in 75% yield as a yellow powder, m.p. 105.5-106.6°C. Next, reduction of the nitro group produced crude 2-aminobenzenesulfon-3'-methoxyanilide in 97% yield. Finally, decomposition of diazonium salt and recrystallization from ethyl acetate / hexane provided methoxy-sultam 50(a) in 28 % yield as a white crystalline solid, m.p.: 168.9-170°C. TLC: Rf = 0.65 (ethyl acetate hexane 1:1).

^{1}H-NMR (DMSO-D_6): 11.32 (bs, 1H), 8.13 (dd, 1H-C_4); 8.12 (dd, 1H-C_{10}); 7.88 (dd,1H-C_1); 7.77 (dt, 1H-C_3); 7.58 (dt,1H-C_2); 6.90 (dd, 1H-C_9); 6.71 (d, 1H-C_7); 3.81 (s, 3H).

b) 4-(8-Methoxy-6H-dibenzo[c,e][1,2]thiazin-6-ylmethyl)piperidine S,S-dioxide.

Starting from methoxy-sultam 50(a) and N-*tert*-butoxycarbonyl-4-(methanesulfonyloxymethyl)piperidine and following typicall procedures described in Examples 2(c) and 2(d), the title piperidine 50(b) hydrochloride was prepared in 86 % yield as a white solid.
Usual basic work-up gave free piperidine 50(b) as a slightly yellow paste.

c) (R,S)-1-(1-Adamantyl)-2-[4-(8-methoxy-6H-dibenzo[c,e][1,2]thiazin-6-ylmethyl)piperidin-1-yl]ethanol S,S-dioxide, hydrochloride.

Reaction of (1-adamantyl)ethylene oxide (0.890 g, 5 mmol) with piperidine 50(b) (1.9 g, 5.3 mmol) was conducted according to the method described in the Example 11(b), but over 48 hrs. Purification by column chromatography (silica gel, methylene chloride / methanol 9:1, TLC: Rf = 0.63) provided t he title aminoalcohol (1.36 g, 51 %) as a pinky solid, m.p.: 193-194°C.
The hydrochloride salt 50(c) was prepared following the usual procedure described in Example 2(d), as a white solid, m.p.: 216-219°C. MS: 371 (M-165).
Anal. Calc'd for $C_{31}H_{41}ClN_2O_4S$ + 2/3 H_2O: C,63.58; H,7.23; N,4.79; Cl,6.07.
Found: C,63.72; H,7.32; N,4.76; Cl,6.15.

EXAMPLE 51

(R,S)-5-[4-[N-[2-(1-Adamantyl)-2-methoxyethyl]-N-methylamino]butyl]-5H-phenanthridin-6-one, hydrochloride.

The O-methylation of the aminoalcohol 10(e) (1.05 g, 2.3mmol) was performed following procedure described in the Example 21. Column chromatography (silica gel, methylene chloride / methanol 10:90, TLC: Rf = 0.2) provided the title methyl ether (0.400 g, 40%) as a viscous oil.
The hydrochloride salt was prepared according to the procedure described in Example 2(d), as a white hygroscopic foam.
MS: 293 (M-179). Anal. Calc'd for $C_{31}H_{40}N_2O_2$ + 1.1 HCl + 1.5 H_2O: C,68.98; H,8.24; N,5.19; Cl,7.22. Found: C,69.14; H,8.30; N,5.20; Cl,7.17.

EXAMPLE 52

(R,S)-1-(1-Adamantyl)-2-[N-methyl-N-[4-(10,11-dihydrodibenz[b,f][1,4]-oxazepin-11-oxo-10-yl)butyl]amino]ethanol, hydrochloride.

a)N-Methyl-N-4-[10-(10,11-dihydrodibenz[b,f][1,4]oxazepin-11-oxo)] butylamine.

Reaction of 10,11-dihydrodibenz[b,f][1,4]oxazepin-11-one (4.22 g, 20 mmol) and mesylate of the alcohol 10(b) (5.6 g, 20 mmol) was performed according to procedure described in Example 10(c) and gave N-*tert*-butoxycarbonyl-N-methyl-N-4-[10-(10,11-dihydrodibenz[b,f][1,4]oxazepin-11-oxo)]butylamine (5.8 g, 73%) as an oil. TLC: Rf = 0.3 (ethyl acetate /hexane 3:7). Subsequent removal of N-Boc protecting group gave amine 52(a) hydrochloride as a white powder, m.p.: 182-184°C. Usual basic work-up provided free amine in 87 % overall yield as a colorless oil.

b) 1-(1-Adamantyl)-2-[N-methyl-N-[4-(10,11-dihydrodibenz[b,f][1,4]-oxazepin-11-oxo-10-yl)butyl]amino]methylketone.

Amine 52(a) (2.0 g, 6.7 mmol) and 1-(bromoacetyl)adamantane (1.85 g, 7.2 mmol) were reacted together, according to procedure described in

Example 1(c), to produce aminoketone 51(b) (2.85 g, 90%) as an orange oil. TLC: Rf = 0.6 (methanol / methylene chloride 1:9).

c) 1-(1-Adamantyl)-2-[N-methyl-N-[4-(10,11-dihydrodibenz[b,f][1,4]-oxazepin-11-oxo-10-yl)butyl]amino]ethanol, hydrochloride.

Reduction of aminoketone 52(b), according to the method described in Example 1(d), gave the title aminoalcohol 52(c) in 95% yield as an oil. TLC: Rf = 0.3 (methanol / methylene chloride 1:9).

The hydrochloride salt 52(c) was prepared according to Example 2(e), but in methylene chloride / diethyl ether, as a white hygroscopic foam.

MS: 309 (M-165). Anal. Calc'd for $C_{30}H_{39}ClN_2O_3$+ 2/3 H_2O: C,68.83; H,7.71; N,5.29; Cl,6.79. Found: C,68.78; H,7.91;N, 5.35; Cl,6.96.

EXAMPLE 53

(R,S)-10-[4-[N-[2-(1-Adamantyl)-2-methoxyethyl]-N-methylamino]butyl]-10,11-dihydrodibenz[b,f][1,4]oxazepin-11-one, hydrochloride.

Reaction of aminoalcohol 52(c) with methanesulfonyl chloride, performed as described in Example 6(a) and followed by column chromatography (silica gel, hexane / ethyl acetate 7:3, TLC: Rf = 0.3), produced corresponding mesylate in 53% yield as a colorless viscous oil.

Methanolysis of the above mesylate was conducted as described in Example 9. Purification by column chromatography (silica gel, methylene chloride / methanol 9:1, TLC: Rf = 0.4) provided methyl ether 53 in 31% yield as a foam.

The title methyl ether 53 hydrochloride was prepared according to the usual procedure described in Example 2(d), as a white hygroscopic foam.

MS: 309 (M-179). Anal. Calc'd for $C_{31}H_{41}ClN_2O_3$+ H_2O: C,68.55; H,7.98; N,5.16; Cl,6.53. Found: C,68.52; H,8.05; N,5.21; Cl,6.53.

EXAMPLE 54

(R,S)-1-(1-Adamantyl)-2-[N-methyl-N-[4-(10,11-dihydrodibenzo[b,f][1,4]-thiazepin-11-oxo-10-yl)butyl]amino]ethanol, hydrochloride.

a) N-Methyl-N-4-[10-(10,11-dihydrodibenzo[b,f][1,4]thiazepin-11-oxo)]

butylamine.

Reaction of 10,11-dihydrodibenzo[b,f][1,4]thiazepin-11-one (7.49 g, 33 mmol) and mesylate derivative of alcohol 10(b) (8.43 g, 30 mmol) was performed according to procedure described in Example 10(c) and gave N-*tert*-butoxycarbonyl-N-methyl-N-4-[10-(10,11-dihydrodibenzo[b,f][1,4]-thiazepin-11-oxo)]butylamine (10.33 g, 83%) as an oil. TLC: Rf = 0.3 (ethyl acetate / hexane 3:7).

Next, removal of N-Boc protecting group gave amine 54(a) hydrochloride as a white powder. Usual basic work-up provided free amine 54(a) in 82% overall yield as a colorless oil.

b) 1-(1-Adamantyl)-2-[N-methyl-N-[4-(10,11-dihydrodibenzo- [b,f][1,4]-thiazepin-11-oxo-10-yl)butyl]amino]methylketone.

Amine 54(a) (6.3 g, 20.5 mmol) and 1-(bromoacetyl) adamantane (5.66 g, 22 mmol) were reacted together, according to procedure described in Example 1(c), to produce aminoketone 54(b) (9.67 g, 96%) as a yellowish oil. TLC: Rf.= 0.7 (methanol / methylene chloride 1:9).

c)(R,S)-1-(1-Adamantyl)-2-[N-methyl-N-[4-(10,11-dihydrodibenzo-[b,f][1,4]-thiazepin-11-oxo-10-yl)butyl]amino]ethanol, hydrochloride.

Reduction of aminoketone 54(b), according to the method described in Example 1(d), gave the title aminoalcohol 54(c) in 52% yield as an oil. TLC: Rf = 0.15 (methanol / methylene chloride 1:12).

The hydrochloride salt was prepared according to the procedure described in Example 2(e), but in methylene chloride / diethyl ether, as a white hygroscopic foam.

MS: 325 (M-165). Anal. Calc'd for $C_{30}H_{39}ClN_2O_2S$+ 2/3 H_2O: C,66.79; H,7.48; N,5.19; Cl,6.58. Found: C,66.91; H,7.78; N,5.06; Cl,6.66.

EXAMPLE 55

(R,S)-10-[4-[N-[2-(1-Adamantyl)-2-methoxyethyl]-N-methylamino]butyl]-10,11-dihydrodibenzo[b,f][1,4]thiazepin-11-one, hydrochloride.

Following the procedure described in Example 6(a), the mesylate

of aminoalcohol 54(c) was prepared in quantitative yield as a colorless viscous oil; TLC: Rf = 0.2 (hexane / ethyl acetate 7:3).

Methanolysis of the above mesylate was performed as described in the Example 9. Column chromatography (silica gel, methylene chloride / methanol 20:1, TLC: Rf = 0.3) furnished methyl ether 55 in 37% yield as a foam.

The title hydrochloride 55 was prepared according to the usual procedure described in Example 2(e), as a hygroscopic foam.

MS: 325 (M-180). Anal. Calc'd for $C_{31}H_{41}ClN_2O_2S$+ 2/3 H_2O: C,67.27; H,7.65; N,5.06; Cl,6.42. Found : C,67.22; H,7.96; N,5.13; Cl,6.31.

PHARMACOLOGY

Some of the compounds of Formula I have been tested according to the following methods.

SIGMA RECEPTORS BINDING ASSAY

The sigma 1 selective binding assay was performed using [^{3}H]-(+) pentazocine (3 nM final, 35 Ci/mmol, New England Nuclear, Dupont de Nemours) as the radioligand according to the method described by D.L. DeHaven-Hudkins, L.C. Fleissner and F.Y. Ford Rice (European Journal of Pharmacology - Molecular Pharmacology Section, 1992, 227, 371-378). Crude P2 membrane fraction was prepared from Guinea pig brain whole membrane preparations as described by E. Weber, M. Sonders, S. Quarum, S. Mc Lean, S. Pou and J. F. Keana (Proc. Natl. Acad. Sci. 1986, 83, 8784-8788). Membrane fractions (0.4 ml) were allowed to incubate 150 min at 37 °C in the presence of various concentrations of the reference compound (Haloperidol 10^{-10} to 10^{-6} M) or of the test ligand (10^{-10} to 10^{-5} M) and the radioligand, in a final volume of 0.5 ml of 50 mM Tris-HCl, pH 7.4. Assays were terminated by rapid filtration through Whatman GF/B filters. Prior to use, filters were soaked in 0.5 % polyethyleneimine for 1 hour. After filtration using a Brandell cell harvester, filters were washed four times with ice cold incubation buffer. Non specific binding was determined using Haloperidol 1 µM. The radioactivity on the filters was determined by scintillation spectrometry using Formula 989 (New England Nuclear, Dupont de Nemours) as scintillator liquid and a counter LS 6000 TA (Becmann). Competition curves were analyzed with the curve fitting program Ligand (G.A. Mc Pherson, Computer Programs in Biomedicine, 1983, 17, 107). Ki and IC 50 values were calculated. Kd value for [^{3}H]-(+) pentazocine was 3nM. Values are averages ± SEM of three experiments, each carried out in duplicate.

The sigma 2 selective binding assay was performed using [^{3}H]-Di-o-Tolyl-Guanidine (DTG) (1 nM final, 37 Ci/mmol, New England Nuclear, Dupont de Nemours) as the radioligand. Crude P2 membrane fraction was prepared

from the livers of male Sprague-Dawley rats according to the method described by X. He, W.D. Bowen, K.S. Lee, W. Williams, D.R. Weinberger and B.R. de Costa (J. Med. Chem. 1993, 36, 566-571). Membrane fractions (0.4 ml) were allowed to incubate 2 hours at 25 °C in the presence of 500 nM of pentazocine and of various concentrations of the reference compound (Haloperidol 10^{-10} to 10^{-6} M) or of the test ligand (10^{-10} to 10^{-5} M) and the radioligand, in a final volume of 0.5 ml of 50 mM Tris-HCl, pH 7.4. Assays were terminated by rapid filtration through Whatman GF/B filters. Prior to use, filters were soaked in 0.5 % polyethyleneimine for 1 hour. After filtration using a Brandell cell harvester, filters were washed four times with ice cold incubation buffer. Non specific binding was determined using Haloperidol 1 µM. Scintillation counting and curve analysis were determined as previously described. Kd value for [^{3}H]-DTG was predetermined and equal to 6.9 nM.

TABLE V :

Example n°	Sigma 1 Ki (nM ± SEM)	Sigma 2 Ki (nM ± SEM)	S2/S1 ratio
Haloperidol	1.5 ± 0.1	36 ± 1	24
1	740 ± 116	10 ± 1	0.01
2	40 ± 6	5.8 ± 0.7	0.14
3	957 ± 65	45 ± 7	0.05
4	230 ± 58	2.4 ± 0.4	0.01
5	1 900 ± 351	4.8 ± 0.6	0.002
9	1 400 ± 58	3.7 ± 0.6	0.003
10	7 333 ± 2000	7.2 ± 0.5	0.001
11	1 933 ± 203	19 ± 8	0.01
19	153 ± 15	1.7 ± 0.5	0.01
20	240 ± 15	1.4 ± 0.2	0.01
21	167 ± 17	6.6 ± 0.8	0.04
22	154 ± 79	2.9 ± 0.8	0.02
23	380 ± 137	3.6 ± 0.8	0.01

TABLE V: (continued)

Example n°	Sigma 1 Ki (nM ± SEM)	Sigma 2 Ki (nM ± SEM)	S2/S1 ratio
24	200 ± 21	4.5 ± 0.8	0.02
25	637 ± 126	4.5 ± 0.2	0.01
26	615 ± 74	25 ± 5	0.04
27	16 ± 5	2 ± 0.5	0.12
28	1 197 ± 257	30 ± 10	0.02
29	370 ± 47	4.5 ± 0.7	0.01
30	1 107 ± 110	6.3 ± 1.9	0.01
31	1 613 ± 387	4.6 ± 2.0	0.003
32	753 ± 37	4.9 ± 1.3	0.01
33	1 097 ± 211	1.5 ± 0.2	0.001
34	1 767 ± 219	1.6 ± 0.5	0.001
35	1 173 ± 474	2.9 ± 0.7	0.002
36	2 600 ± 351	2.2 ± 0.5	0.001
37	300 ± 105	3.7 ± 0.6	0.01
38	2 533 ± 674	4.2 ± 0.7	0.002
39	250 ± 15	2.3 ± 0.3	0.01
40	200 ± 15	6.9 ± 0.4	0.03
41	913 ± 67	0.85 ± 0.16	0.001
42	1 150 ± 161	1 ± 0.2	0.001
43	923 ± 390	3.1 ± 0.9	0.003
44	877 ± 320	4.9 ± 1.8	0.006
45	1 900 ± 451	4.3 ± 0.2	0.002
46	1 423 ± 345	3.1 ± 0.5	0.002
47	957 ± 225	4.1 ± 0.3	0.004
48	210 ± 46	2.5 ± 0.3	0.01
49	4 200 ± 2 300	4.6 ± 1.2	0.001
50	1 290 ± 274	3.2 ± 0.6	0.002
51	9 833 ± 1 102	6.2 ± 0.8	0.001
52	3 900 ± 1 300	10.7 ± 1.3	0.003
53	2 900 ± 700	5.1 ± 0.9	0.002
54	2 100 ± 500	17.0 ± 4.6	0.008
55	7 200 ± 1900	9.9 ± 0.6	0.001

The binding data presented in the above table, based on at least 3 determinations, show that the molecules of the present invention are moderatly to highly potent sigma 2 ligands and that they show a high selectivity for this site.

The binding of these compounds to dopaminergic receptors was measured according to the method described by M. Terai, K. Hidaka and Y. Nakamura [Eur. J. Pharmacol. 1989, 173, 177] using rat striata. The affinity of these compounds towards serotoninergic 5-HT2 receptors was also evaluated following the method described by J.E. Leysen, C.J.E. Niemegeers, J.M. Van Nueten and P.M. Laduron [Molecular Pharmacology 1982, 21, 301-314] using rat frontal cortex. Results are presented in Table VI :

TABLE VI :

Example n°	Dopamine D2 IC50 (nM)	5-HT2 IC50 (nM)
1	> 10 000	6 200
2	> 10 000	2 500
3	> 10 000	> 10 000
4	7 200	1 750
5	> 10 000	6 000
9	> 10 000	7 000
10	> 10 000	5 100
11	> 10 000	3 200
19	> 10 000	940
20	3 300	3 400
21	2 200	4 400
22	1 700	3 100
23	4 200	3 900
24	4 100	5 500
25	6 400	8 100
26	6 600	10 000

TABLE VI : (continued)

Example n°	Dopamine D2 IC50 (nM)	5-HT2 IC50 (nM)
27	6 600	1 800
28	940	360
29	1 200	240
30	4 800	640
31	850	100
32	800	80
33	5 900	1 760
34	3 900	2 200
35	3 500	1 200
36	6 900	410
37	6 300	130
38	7 300	4 800
39	3 500	4 700
40	690	210
41	4 400	400
42	3 300	550
43	9 200	310
44	1 100	140
45	9 000	310
46	> 10 000	300
47	5 100	310
48	4 000	500
49	3 000	66
50	3 500	150
51	> 10 000	8 200
52	> 10 000	1 700
53	> 10 000	1 500
54	> 10 000	4 600
55	> 10 000	6 900

Additionally, some compounds of the invention were tested on alpha 1 adrenergic, beta 1 and 2 adrenergic, D1, 5-HT1, 5-HT1A, 5-HT3 and

phencyclidine receptors. For most compounds, the selectivity was very high : IC50 X/ IC50 Sigma 2 > 100. X : D1, D2, 5-HT1, 5-HT1A, 5-HT2, 5-HT3, alpha1 adrenergic, beta 1 and 2 adrenergic and phencyclidine receptors.

IN VIVO PHARMACOLOGY

The psychotropic properties of the compounds have been determined by some standard tests exploring dopaminergic, serotonergic and glutamatergic mechanisms, which are all involved in schizophrenic pathogenia.

Mescaline induced scratching in Mice

This is a modification of the method of Cook L., Tam S.W. and Rohrbach K.W. [J. Pharmacol. Exp. Ther. 1992, 263, 1159-1166]. In mice, compounds (10 animals /dose) were administered per os 60 min before 10 mg/kg i.p. of Mescaline. 10 minutes after the challenge, mice were observed during a 10 min period and the number of scratching were counted. The ED50 was defined as the dose of the test compound that protected 50 % of the scratching number.

TABLE VII :

EXAMPLE n°	Mouse antimescaline ED50 (mg/kg, per os)
1	0.3
4	0.2

Table VII shows that compounds of the invention strongly antagonize the scratching behavior in mice. In this tests, these compounds had excellent oral psychotropic activity.

TOXICITY

The study of the toxicity of the products of the invention was determined on mice by oral administration by the approximate determination of their LD 50. It has been observed that the products of the invention generally had an acute toxicity or LD 50 greater than 1 000 mg/Kg. No cataleptic effect was observed with these compounds.

FORMULATION EXAMPLES

The pharmaceutical formulations of the invention may be prepared by conventional methods in the art.

Typical examples of recipes for the formulation of the invention are as follows:

1) Tablets :

Compound of the example 2	5 to 50 mg
DiCalcium phosphate	20 mg
Lactose	30 mg
Talcum	10 mg
Magnesium stearate	5 mg
Potato starch	ad 200 mg

in this example, the compound 2 can be replaced by the same amount of any of the described examples 1 to 55.

2) Suspension :

An aqueous suspension is prepared for oral administration so that each 1 milliliter contains 1 to 5 mg of one of the described example, 50 mg of sodium carboxymethyl cellulose, 1 mg of sodium benzoate , 500 mg of sorbitol and water ad 1 ml.

3) Injectable :

A parenteral composition is prepared by stirring 1.5 % by weight of active ingredient in 10 % by volume propylene glycol and water.

4) Ointment :

Compound of the example 2	5 to 1000 mg
Stearyl alcohol	3 g
Lanoline	5 g
White petroleum	15 g
Water	ad 100 g

in this example, the compound 2 can be replaced by the same amount of any of the described examples 1 to 55.

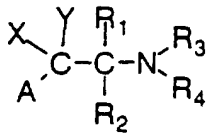
Reasonable variations are not to be regarded as a departure from the scope of the invention. It will be obvious that the thus described invention may be varied in many ways by those skilled in the art.

Industrial Applicability

The compounds of the present invention exhibit a high selectivity and high affinity for sigma 2 receptor and therefore are useful in the treatment of central nervous system disorders as well as other disorders modulated by this receptor.

CLAIMS

1. A compound which conforms to the general formula I :



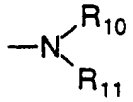
(1)

When X represents cycloalkylalkyl or adamantyl, Y represents hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, adamantyl, aryl, arylalkyl, heteroaryl or heteroarylalkyl; wherein each of said aryl and heteroaryl groups may optionally be substituted with one or more substituents, each of the said substituents being independently selected from halo, nitro, cycloalkyl, alkenyl, alkyl optionally substituted with one to three fluorine atoms, hydroxy, alkoxy optionally substituted with one to three fluorine atoms, phenyl, amino, alkylamino, carbamoyl, sulfamoyl, carboxyalkyl, cyano or alkynyl;

When X represents cycloalkyl, Y represents hydrogen, alkyl, alkenyl or cycloalkyl;

A represents the group -O- R_9 in which R_9 represents hydrogen, alkyl, cycloalkyl, cycloalkylalkyl, alkenyl, aryl, arylalkyl, hydroxyalkyl, carboxyalkyl or carboxyaryl;

or A represents the group



R_{10} and R_{11} represent independently hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, hydroxyalkyl, carboxyalkyl, haloalkyl, haloalkoxyalkyl, aryl, arylalkyl, heteroaryl or heteroarylalkyl; each of the said aryl and heteroaryl groups may optionally be substituted with one or more substituents, each of the said

substituents being independently selected from halo, nitro, cycloalkyl, alkenyl, alkyl optionally substituted with from one to three fluorine atoms, hydroxy, alkoxy optionally substituted with one to three fluorine atoms, phenyl, amino, alkylamino, carboxy, carbamoyl, sulfamoyl, carboxyalkyl, cyano or alkynyl;

R_{10} and R_{11} taken together may form a ring corresponding to the formula :

$$-(CH_2)m-D-(CH_2)m-$$

where D represents a single bond, oxygen, sulfur or a nitrogen atom substituted by hydrogen, alkyl, cycloalkyl, alkenyl, cycloalkylalkyl, aryl or arylalkyl;

m is a number selected from 1 to 3;

R_{10} and R_{11} taken together with the nitrogen atom may form a 3-10-atom unsaturated heterocyclic ring which optionally contains 1 to 4 further heteroatom selected from oxygen, nitrogen and sulfur; such heterocyclic group may optionally be substituted with one or more substituents, each of the said substituents being independently selected from halo, nitro, cycloalkyl, alkenyl, alkyl optionally substituted with one to three fluorine atoms, hydroxy, alkoxy optionally substituted with one to three fluorine atoms, phenyl, amino, alkylamino, carbamoyl, sulfamoyl, carboxy,carboxyalkyl, cyano or alkynyl;

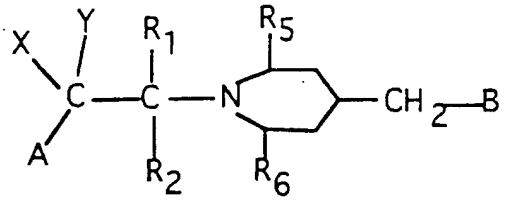
or Y and A taken together may form oxo or hydroxyimino;

R_1 and R_2 which may be the same or different, are hydrogen, alkyl, cycloalkyl, hydroxyalkyl or alkenyl;

R_3 represents alkyl, cycloalkyl, hydroxyalkyl or alkenyl;

R_4 represents the group $-(CH_2)p-B$ where p is a number selected from 3 to 8;

or R_3 and R_4 together with the intervening nitrogen atom represent a piperidine ring which is substituted as depicted in formula **(II)** :

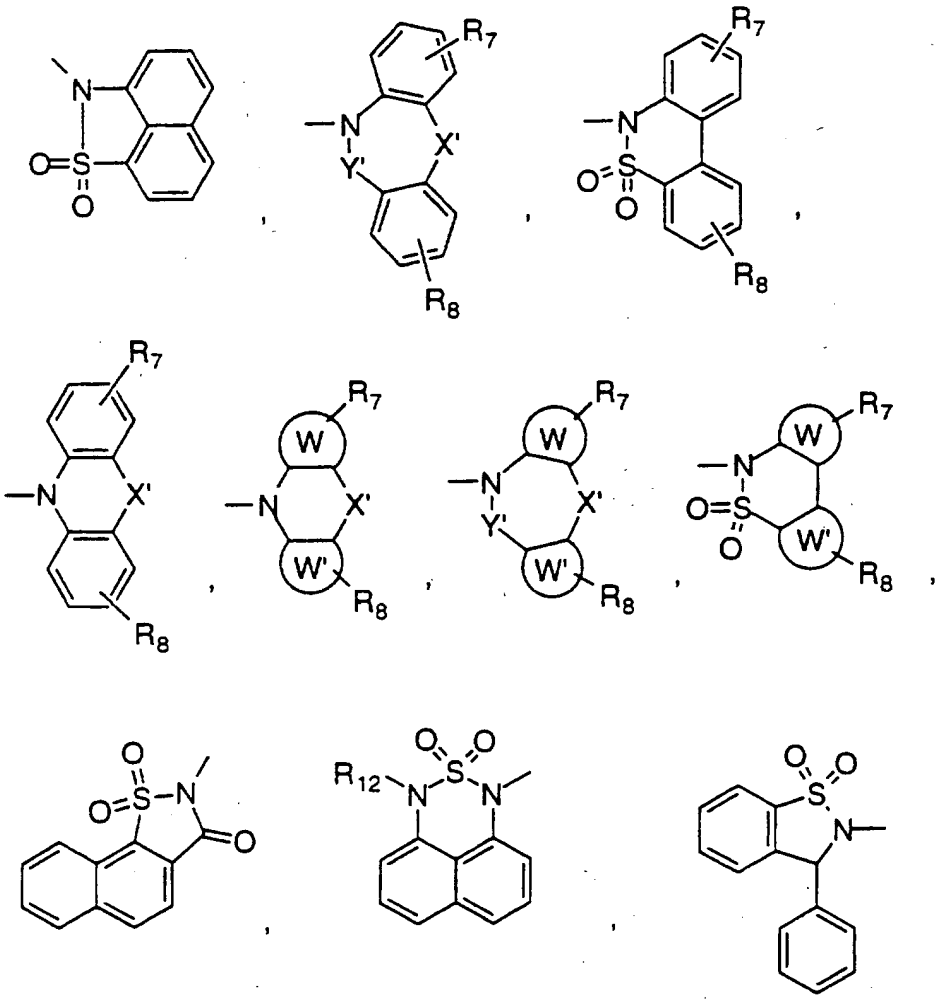


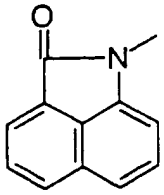
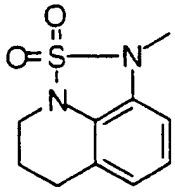
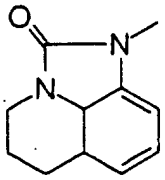
(II)

where R_5 and R_6 represent independently hydrogen or alkyl;

or R_5 and R_6 together with the intervening atom represent a 5 to 7 heterocyclic ring;

B is a heteroaryl group of formula



 ,  or  .

R_7 and R_8 are independently selected from hydrogen, halo, nitro, cycloalkyl, alkenyl, alkyl optionally substituted with one to three fluorine atoms, hydroxy, alkoxy optionally substituted with one to three fluorine atoms, phenyl, amino, alkylamino, carbamoyl, sulfamoyl, carboxyalkyl, cyano or alkynyl;

R_{12} is selected from hydrogen or alkyl;

X' represents a single bond, $-CH_2-$, $-CH=CH-$, $-CH_2-CH_2-$, S, $-S-CH_2-$, $-S(O)-$, $-S(O)_2-$, $-S(O)-CH_2-$, $-S(O)_2-CH_2-$, O, $-O-CH_2-$, $N(R_{13})$, $-N(R_{13})-CH_2-$, $-N(R_{13})-S(O)_2-$, C(=O), $-C(=O)-CH_2-$, $-C(=O)-O-$ or $-C(=O)-N(R_{13})-$;

Y' represents $-CH_2-$ or C(=O) ;

W and W' represent independently a benzene ring or heteroaryl group of 5 to 7 atoms which contains one oxygen atom , one sulfer atom or one or two nitrogen atoms, provided that at least one of W and W' is heteroaryl group.

R_{13} represents hydrogen or alkyl.;

or a pharmaceutically acceptable salt, hydrates or solvates of such compounds.

2. A compound according to claim 1 wherein :

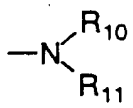
When X represents C_3-C_6 cycloalkyl-C_1-C_3-alkyl or adamantyl, Y represents hydrogen, C_1-C_6 alkyl, C_3-C_6 alkenyl, C_3-C_6 alkynyl, C_3-C_6 cycloalkyl, C_3-C_6 cycloalkyl-C_1-C_3-alkyl, adamantyl, aryl selected from phenyl and naphthyl, aryl-C_1-C_3-alkyl; wherein each of said aryl group may optionally

be substituted with one to three substituents, each of the said substituents being independently selected from halo, nitro, C3-C6 cycloalkyl, C3-C6 alkenyl, C1-C6 alkyl optionally substituted with one to three fluorine atoms, hydroxy, C1-C6 alkoxy optionally substituted with one to three fluorine atoms, phenyl, amino, C1-C6 alkylamino, carbamoyl, sulfamoyl, carboxy-C1-C6-alkyl, cyano or C3-C6 alkynyl;

When X represents C3-C6 cycloalkyl, Y represents hydrogen, C1-C6 alkyl, C3-C6 alkenyl or C3-C6 cycloalkyl;

A represents the group -O-R9 in which R9 represents hydrogen, C1-C6 alkyl, C3-C6 cycloalkyl, C3-C6 cycloalkyl-C1-C3-alkyl, C3-C6 alkenyl, phenyl, phenyl-C1-C3-alkyl, hydroxy-C2-C6-alkyl, carboxy-C1-C3-alkyl or carboxyphenyl;

or A represents the group



R_{10} and R_{11} represent independently hydrogen, C1-C6 alkyl, C3-C6 alkenyl, C3-C6 alkynyl, C3-C6 cycloalkyl, phenyl or phenyl-C1-C3-alkyl; phenyl group may optionally be substituted with one to three substituents, each of the said substituents being independently selected from halo, nitro, C1-C6 alkyl, hydroxy, amino, carboxy or cyano;

R_{10} and R_{11} taken together may form a ring corresponding to the formula :

$$-(CH_2)m-D-(CH_2)m-$$

where D represents a single bond, oxygen, sulfur or a nitrogen atom substituted by hydrogen or C1-C6 alkyl;

m is a number selected from 1 to 3;

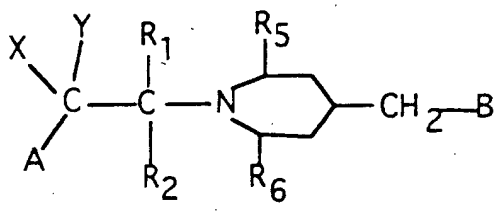
or Y and A taken together may form oxo or hydroxyimino;

R_1 and R_2 which may be the same or different, are hydrogen, C_1-C_3 alkyl, C_3-C_6 cycloalkyl, hydroxy-C_2-C_3 alkyl or C_3-C_6 alkenyl.

R_3 represents C_1-C_3 alkyl, C_3-C_6 cycloalkyl, hydroxy-C_2-C_3-alkyl or C_3-C_6-alkenyl;

R_4 represents the group -$(CH_2)p$-B where p is a number selected from 3 to 6;

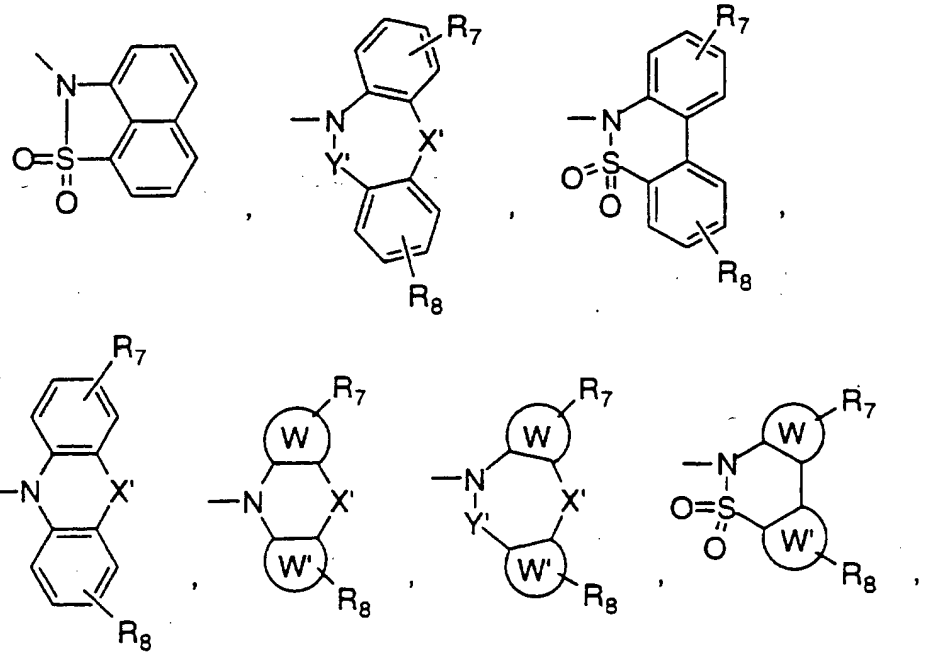
or R_3 and R_4 together with the intervening nitrogen atom represent a piperidine ring which is substituted as depicted in formula **(II)** :

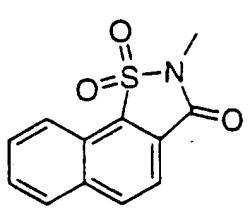
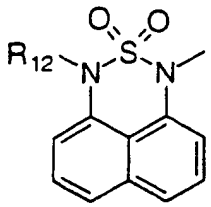
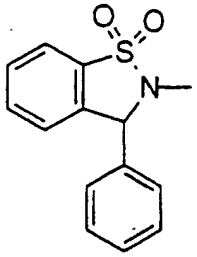
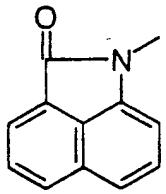
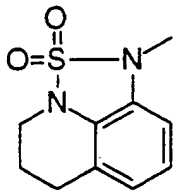
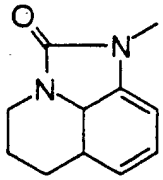


(II)

where R_5 and R_6 represent independently hydrogen or C_1-C_3 alkyl;

B is a heteroaryl group of formula








or


R_7 and R_8 are independently selected from hydrogen, halo, nitro, C_1-C_6 alkyl optionally substituted with one to three fluorine atoms, hydroxy or C_1-C_6 alkoxy optionally substituted with one to three fluorine atoms;

R_{12} is selected from hydrogen or C_1-C_6 alkyl;

X' represents a single bond, -CH_2-, -CH=CH-, -CH_2-CH_2-, S, -S-CH_2-, -S(O)-, -$S(O)_2$-, -S(O)-CH_2-, -$S(O)_2$-CH_2-, O, -O-CH_2-, N(R_{13}), -N(R_{13})-CH_2-, -N(R_{13})-$S(O)_2$-, C(=O), -C(=O)-CH_2-, -C(=O)-O- or -C(=O)-N(R_{13})-;

Y' represents -CH_2- or C(=O) ;

W and W' represent independently a benzene ring or heteroaryl group of 5 to 7 atoms which contains one oxygen atom , one sulfer atom or one or two nitrogen atoms, provided that at least one of W and W' is heteroaryl group;

R_{13} represents hydrogen or C_1-C_6 alkyl;

or a pharmaceutically acceptable salt, hydrates or solvates of such compounds.

3. A compound according to claim 1 or 2 wherein

When X represents C3-C6 cycloalkyl-C1-C3-alkyl, adamantyl or C3-C6 cycloalkyl, Y represents hydrogen, C1-C6 alkyl, C3-C6 alkenyl or C3-C6 cycloalkyl.;

A represents the group -O-R9 in which R9 represents hydrogen, C1-C4 alkyl, C3-C6 alkenyl or hydroxy- C2-C4-alkyl;

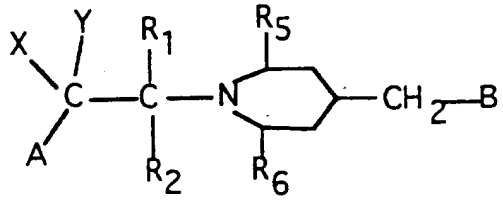
or Y and A taken together may form oxo or hydroxyimino;

R_1 and R_2 which may be the same or different, are hydrogen or C1-C3 alkyl;

R_3 represents C1-C3 alkyl or C3-C6 alkenyl;

R_4 represents the group -$(CH_2)_p$-B where p is a number selected from 3 to 6;

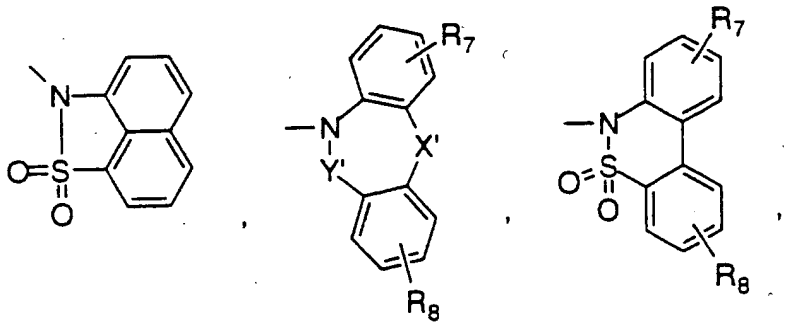
or R_3 and R_4 together with the intervening nitrogen atom represent a piperidine ring which is substituted as depicted in formula **(II)** :

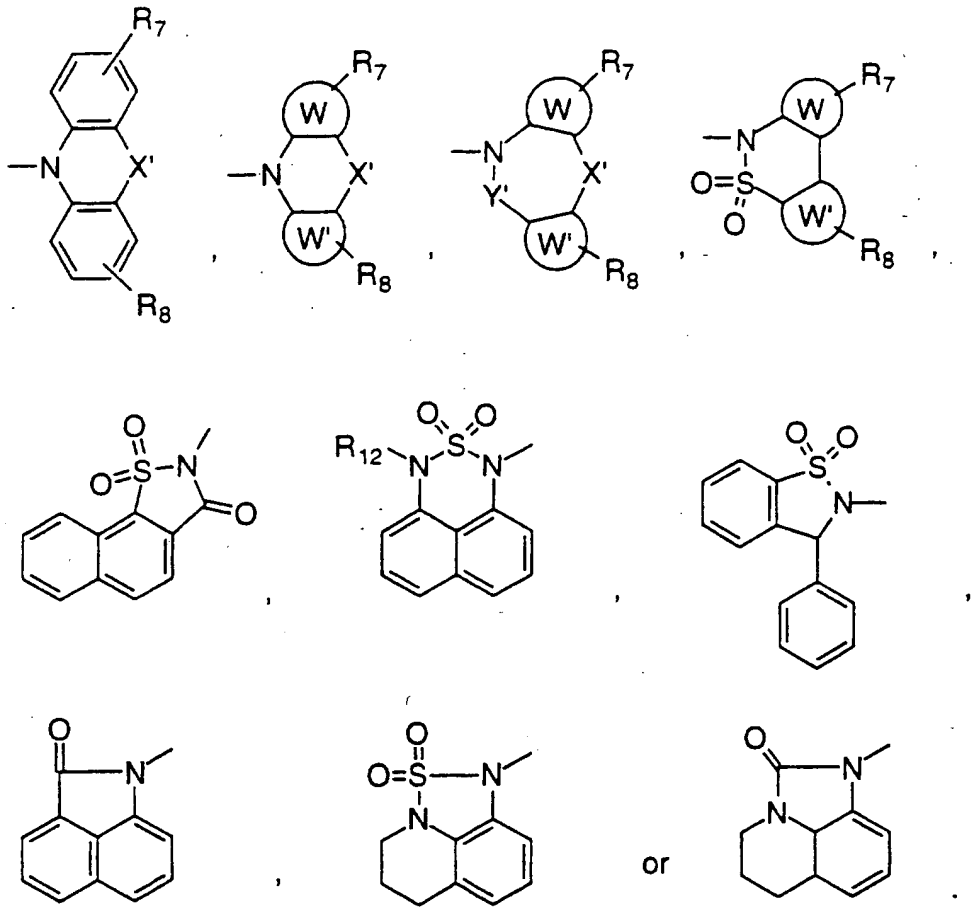


(II)

where R_5 and R_6 represent hydrogen or methyl;

B is a heteroaryl group of formula





R_7 and R_8 are independently selected from hydrogen, halo, nitro, C_1-C_6 alkyl optionally substituted with one to three fluorine atoms, hydroxy or C_1-C_6 alkoxy optionally substituted with one to three fluorine atoms;

R_{12} is selected from hydrogen or C_1-C_6 alkyl;

X' represents a single bond, $-CH_2-$, $-CH=CH-$, $-CH_2-CH_2-$, S, $-S-CH_2-$, $-S(O)-$, $-S(O)_2-$, $-S(O)-CH_2-$, $-S(O)_2-CH_2-$, O, $-O-CH_2-$, $N(R_{13})$, $-N(R_{13})-CH_2-$, $-N(R_{13})-S(O)_2-$, C(=O), -C(=O)-CH2-, -C(=O)-O- or $-C(=O)-N(R_{13})-$;

Y' represents $-CH_2-$ or C(=O) ;

W and W' represent independently a benzene ring or heteroaryl group of 5 to 7 atoms which contains one oxygen atom , one sulfer atom or one or two nitrogen atoms, provided that at least one of W and W' is heteroaryl group;

R_{13} represents hydrogen or C_1-C_6 alkyl;

or a pharmaceutically acceptable salt, hydrates or solvates of such compounds.

4. A compound according to claim 1 or 2 wherein

When X represents C_3-C_6 cycloalkyl-C_1-C_3-alkyl, adamantyl or C_3-C_6 cycloalkyl, Y represents hydrogen, C_1-C_6 alkyl, C_3-C_6 alkenyl or C_3-C_6 cycloalkyl.;

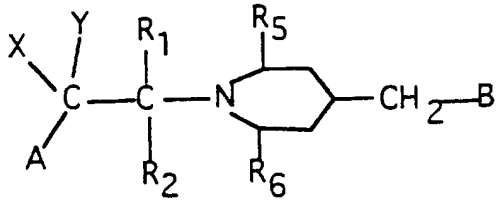
A represents amino, C_1-C_3 alkylamino, phenyl-C_1-C_3-alkylamino, C_3-C_6 alkenylamino, C_2-C_6 dialkylamino, C_4-C_5 cycloalkylamino, C_4-C_7 alkylalkenylamino, piperidino, piperazino, C_1-C_3 alkylpiperazino or morpholino;

R_1 and R_2 which may be the same or different, are hydrogen or C_1-C_3 alkyl;

R_3 represents C_1-C_3 alkyl or C_3-C_6 alkenyl;

R_4 represents the group -(CH_2)p-B where p is a number selected from 3 to 6;

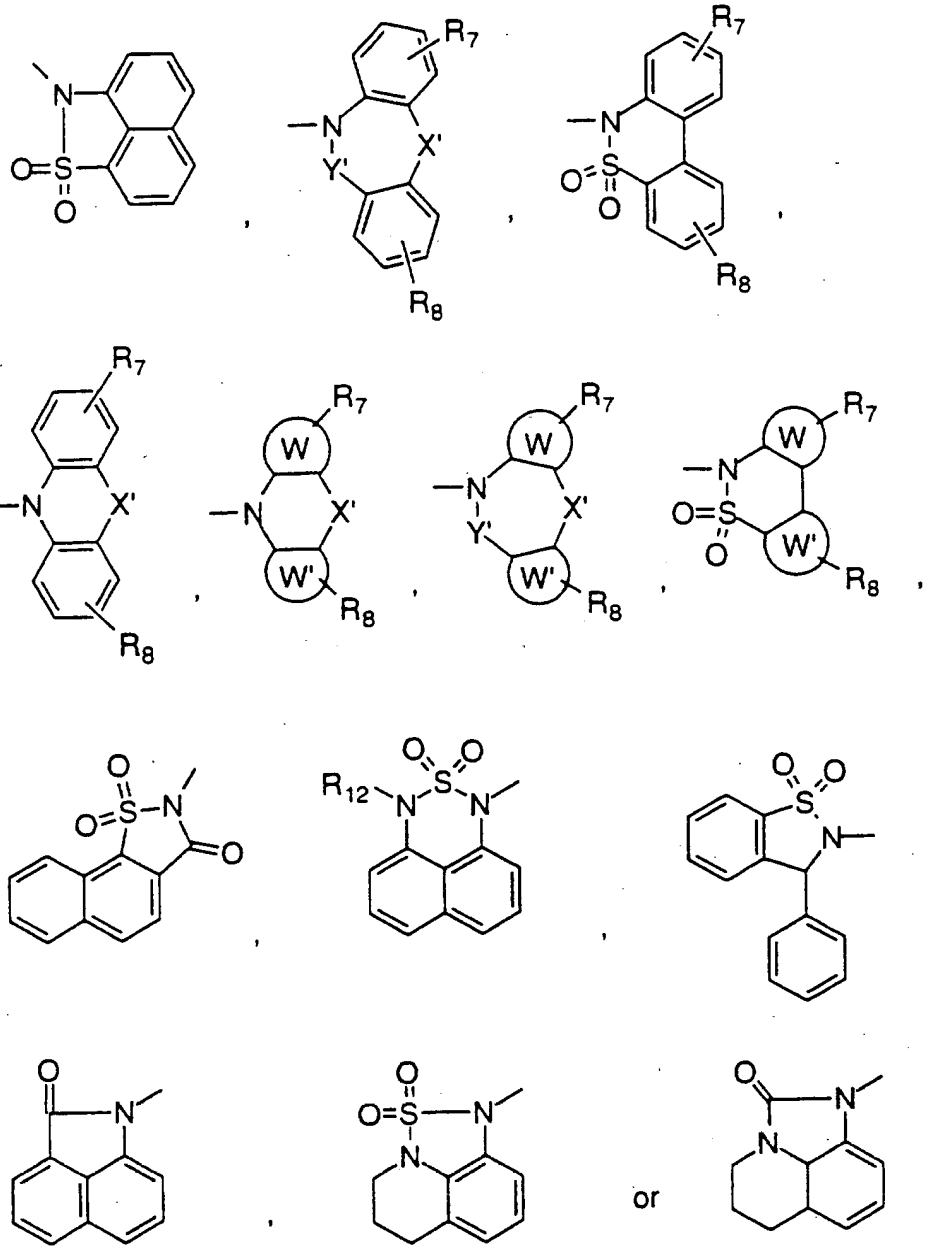
or R_3 and R_4 together with the intervening nitrogen atom represent a piperidine ring which is substituted as depicted in formula **(II)** :



(II)

where R_5 and R_6 represent hydrogen or methyl;

B is a heteroaryl group of formula



or

5

R_7 and R_8 are independently selected from hydrogen, halo, nitro, C1-C6 alkyl optionally substituted with one to three fluorine atoms, hydroxy or C1-C6 alkoxy optionally substituted with one to three fluorine atoms;

10

R_{12} is selected from hydrogen or C_1-C_6 alkyl;

X' represents a single bond, $-CH_2-$, $-CH=CH-$, $-CH2-CH_2-$, S, $-S-CH_2-$, $-S(O)-$, $-S(O)_2-$, $-S(O)-CH_2-$, $-S(O)_2-CH_2-$, O, $-O-CH2-$, $N(R_{13})$, $-N(R_{13})-CH_2-$, $-N(R_{13})-S(O)_2-$, C(=O), $-C(=O)-CH_2-$, $-C(=O)-O-$ or $-C(=O)-N(R_{13})-$;

Y' represents $-CH_2-$ or C(=O) ;

W and W' represent independently a benzene ring or heteroaryl group of 5 to 7 atoms which contains one oxygen atom , one sulfer atom or one or two nitrogen atoms, provided that at least one of W and W' is heteroaryl group;

R_{13} represents hydrogen or C_1-C_6 alkyl;

or a pharmaceutically acceptable salt, hydrates or solvates of such compounds.

5. A compound according to claim 1, 2, 3 or 4 which can exist as optical isomers, wherein said compounds are both the racemic mixture or the individual optical isomers.

6. A compound according to claims 1 to 5, wherein said compound is selected from :

(R,S)-1-(1-Adamantyl)-2-[N-methyl-N-[4-(2H-naphth[1,8-*cd*]isothiazol-2-yl)butyl]amino]ethanol S,S-dioxide;

(R,S)-2-[[1-[2-(1-Adamantyl)-2-oxoethyl]-4-piperidinyl]methyl]-2H-naphth[1,8-*cd*]isothiazole 1,1-dioxide;

(R,S)-2-[[1-[2-(1-Adamantyl)-2-oximinoethyl]-4-piperidinyl]methyl]-2H-naphth[1,8-*cd*]isothiazole 1,1-dioxide;

(R,S)-1-(1-Adamantyl)-2-[4-(2H-naphth[1,8-*cd*]isothiazol-2-ylmethyl)piperidin-1-yl]ethanol S,S-dioxide;

(R,S)-1-(1-Adamantyl)-2-[4-(9-carbazolyl)methylpiperidin-1-yl]ethanol;

(R,S)-1-(1-Adamantyl)-2-[N-methyl-N-[4-(2H-naphth[1,8-*cd*]isothiazol-2-yl)butyl]amino]ethylamine S,S-dioxide;

(R,S)-1-(1-Adamantyl)-N-methyl-2-[N-methyl-N-[4-(2H-naphth[1,8-*cd*]isothiazol-2-yl)butyl]amino]ethylamine S,S-dioxide;

(R,S)-2-(1-Adamantyl)-N-methyl-N-[4-(2H-naphth[1,8-*cd*]isothiazol-2-yl)butyl]-2-pyrrolidin-1-ylethylamine S,S-dioxide;

(R,S)-2-[4-[N-[2-(1-Adamantyl)-2-methoxyethyl]-N-methylamino]butyl]-2H-naphth[1,8-*cd*]isothiazole 1,1-dioxide;

(R,S)-1-(1-Adamantyl)-2-[N-methyl-N-[5H-phenanthridin-6-oxo-5-yl]butyl]-amino]ethanol;

(R,S)-1-(1-Adamantyl)-2-[N-methyl-N-[4-(6H-dibenzo[*ce*][1,2]thiazin-6-yl)butyl]amino]ethanol S,S-dioxide;

(R,S)-1-(1-Adamantyl)-2-[4-(2H-naphth[1,8-*cd*]isothiazol-2-ylmethyl)piperidin-1-yl]ethylamine S,S-dioxide;

(R,S)-1-(1-Adamantyl)-N-methyl-2-[4-(2H-naphth[1,8-*cd*]isothiazol-2-ylmethyl)piperidin-1-yl]ethylamine S,S-dioxide;

(R,S)-2-[1-[2-(1-Adamantyl)-2-morpholin-4-ylethyl]piperidin-4-ylmethyl]-2H-naphth[1,8-*cd*]isothiazole 1,1-dioxide;

(R,S)-2-[1-[2-(1-Adamantyl)-2-pyrrolidin-1-ylethyl]piperidin-4-ylmethyl]-2H-naphth[1,8-*cd*]isothiazole 1,1-dioxide;

(R,S)-2-[1-[2-(1-Adamantyl)-2-(4-methyl)piperazin-1-ylethyl]piperidin-4-ylmethyl]-2H-naphth[1,8-*cd*]isothiazole 1,1-dioxide;

(R,S)-1-(1-Adamantyl)-N,N-diethyl-2-[4-(2H-naphth[1,8-*cd*]isothiazol-2-ylmethyl)piperidin-1-yl]ethylamine S,S-dioxide;

(R,S)-1-(1-Adamantyl)-N-allyl-N-methyl-2-[4-(2H-naphth[1,8-*cd*]isothiazol-2-ylmethyl)piperidin-1-yl]ethylamine S,S-dioxide;

(R,S)-2-[1-[2-(1-Adamantyl)-2-methoxyethyl]piperidin-4-ylmethyl]-2H-naphth[1,8-*cd*]isothiazole 1,1-dioxide;

(R,S)-2-[1-[2-(1-Adamantyl)-2-ethoxyethyl]piperidin-4-ylmethyl]-2H-naphth[1,8-*cd*]isothiazole 1,1-dioxide;

(R,S)-1-(1-Adamantyl)-1-methyl-2-[4-(2H-naphth[1,8-*cd*]isothiazol-2-ylmethyl)piperidin-1-yl]ethanol S,S-dioxide;

(R,S)-1-Cyclohexyl-2-[4-(2H-naphth[1,8-*cd*]isothiazol-2-ylmethyl)piperidin-1-yl]ethanol S,S-dioxide;

(R,S)-1-(1-Adamantyl)-2-[4-(2-chlorophenothiazin-10-ylmethyl)piperidin-1-yl]-ethanol;

(R,S)-1-(1-Adamantyl)-2-[4-(phenothiazin-10-ylmethyl)piperidin-1-yl]ethanol;

(R,S)-1-(1-Adamantyl)-2-[4-(phenoxazin-10-ylmethyl)piperidin-1-yl]ethanol;

(R,S)-1-(1-Adamantyl)-2-[4-(5H-dibenz[b,f]azepin-5-ylmethyl)piperidin-1-yl]ethanol;

(R,S)-1-(1-Adamantyl)-2-[4-(10,11-dihydro-5H-dibenz[b,f]azepin-5-ylmethyl)-piperidin-1-yl]ethanol;

(R,S)-1-(1-Adamantyl)-2-[4-(5H-phenanthridin-6-oxo-5-ylmethyl)piperidin-1-yl]ethanol;

(R,S)-1-(1-Adamantyl)-2-[4-(10,11-dihydrodibenz[b,f][1,4]oxazepin-11-oxo-10-ylmethyl)piperidin-1-yl]ethanol;

(R,S)-1-(1-Adamantyl)-2-[4-(10,11-dihydrodibenzo[b,e][1,4]diazepin-11-oxo-10-ylmethyl)piperidin-1-yl]ethanol;

(R,S)-1-(1-Adamantyl)-2-[4-(10,11-dihydrodibenzo[b,f][1,4]thiazepin-11-oxo-10-ylmethyl)piperidin-1-yl]ethanol;

(R,S)-1-(1-Adamantyl)-2-[4-(5,6,11,12-tetrahydrodibenz[b,f]azocin-6-oxo-5-ylmethyl)piperidin-1-yl]ethanol;

(R,S)-1-(1-Adamantyl)-2-[4-(5,6,11,12-tetrahydrodibenz[b,f]azocin-5-ylmethyl)piperidin-1-yl]ethanol;

(R,S)-1-(1-Adamantyl)-2-[4-(6H-dibenzo[c,e][1,2]thiazin-6-ylmethyl)piperidin-1-yl]ethanol S,S-dioxide;

(S)-6-[1-[2-(1-Adamantyl)-2-methoxyethyl]piperidin-4-ylmethyl]-6H-dibenzo[c,e][1,2]thiazine 5,5-dioxide;

(R)-6-[1-[2-(1-Adamantyl)-2-methoxyethyl]piperidin-4-ylmethyl]-6H-dibenzo[c,e][1,2]thiazine 5,5-dioxide;

(R,S)-1-(1-Adamantyl)-2-[4-(7-fluoro-6H-dibenzo[c,e][1,2]thiazin-6-ylmethyl)-piperidin-1-yl]ethanol S,S-dioxide;

(R,S)-1-(1-Adamantyl)-2-[4-(8-fluoro-6H-dibenzo[c,e][1,2]thiazin-6-ylmethyl)-piperidin-1-yl]ethanol S,S-dioxide;

(R,S)-1-(1-Adamantyl)-2-[4-(9-fluoro-6H-dibenzo[c,e][1,2]thiazin-6-ylmethyl)-piperidin-1-yl]ethanol S,S-dioxide;

(R,S)-1-(1-Adamantyl)-2-[N-methyl-N-[4-(10,11-dihydrodibenz[b,f][1,4]-oxazepin-11-oxo-10-yl)butyl]amino]ethanol;

(R,S)-10-[4-[N-[2-(1-Adamantyl)-2-methoxyethyl]-N-methylamino]butyl]-10,11-dihydrodibenz[b,f][1,4]oxazepin-11-one;

(R,S)-1-(1-Adamantyl)-2-[N-methyl-N-[4-(10,11-dihydrodibenzo[b,f][1,4]-thiazepin-11-oxo-10-yl)butyl]amino]ethanol;

(R,S)-10-[4-[N-[2-(1-Adamantyl)-2-methoxyethyl]-N-methylamino]butyl]-10,11-dihydrodibenzo[b,f][1,4]thiazepin-11-one;

(R,S)-5-[4-[N-[2-(1-Adamantyl)-2-methoxyethyl]-N-methylamino]butyl]-5H-phenanthridin-6-one;

(R,S)-1-(1-Adamantyl)-2-[4-(8-chloro-6H-dibenzo[c,e][1,2]thiazin-6-ylmethyl)-piperidin-1-yl]ethanol S,S-dioxide;

(R,S)-1-(1-Adamantyl)-2-[4-(8-methoxy-6H-dibenzo[c,e][1,2]thiazin-6-ylmethyl)-piperidin-1-yl]ethanol S,S-dioxide.

7. A pharmaceutical composition comprising a therapeutically effective amount of a compound according to claims 1 to 6 and pharmaceutically acceptable carriers and/or excipients.

8. A method of treating or preventing a condition in a mammal, including a human, the treatment or prevention of which is affected or facilitated by the neuromodulatory effect of sigma 2 ligands, comprising administering to a mammal in need of such treatment or prevention, an effective amount of a compound according to claims 1 to 6.

9. A method useful for treating or preventing central nervous system disorders and cardiovascular disorders selected from the group consisting of : anxiety, depression or dysthymic disorders, psychosis, pain, dyskinesia, ischaemia-induced brain disorders, convulsions, stroke, epilepsy, dementia, parkinsonism, neuropathological disorders, memory impairment, hypertension, arrhythmia and angina, comprising administering an effective amount of a compound according to claims 1 to 6.

10. A method according to claim 8, wherein the sigma 2 receptor ligand has an inhibition constant Ki for sigma 2 receptor of at least 50 nM and

has at least a 5 fold greater affinity for sigma 2 receptor relative to sigma 1 receptor and to dopaminergic, serotonin, PCP and adrenergic receptors.

11.The method according to claims 8 to 10 wherein the disease is psychosis.

12. The method according to claims 8 to 10 wherein the disease is anxiety.

13. A method of treating amphetamine abuse or addiction in a mammal, comprising administering to a mammal in need of such treatment, an effective amount of a compound according to claims 1 to 6.

14. The method according to claims 8 to 10 wherein the disease is ischaemia-induced brain disorders.

15. A method according to claims 8 to 10 wherein the disease is a cardiovascular disease like hypertension, arrhythmia or angina.

INTERNATIONAL SEARCH REPORT

al Application No
PCT/JP 95/01600

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D275/06 A61K31/425 C07D417/06 C07D401/06 C07D221/12
C07D413/06 C07D279/02

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	EP,A,0 429 341 (RHONE-POULENC SANTE) 29 May 1991 cited in the application see claims ---	1-5,8-15
Y	EP,A,0 350 403 (RHONE-POULENC SANTE) 10 January 1990 cited in the application see claims ---	1-5,8-15
Y	EP,A,0 433 149 (RHONE-POULENC SANTE) 19 June 1991 see claims ---	1-5,8-15
Y	FR,A,2 675 801 (RHONE-POULENC RORER) 30 October 1992 see claims ---	1-5,8-15

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
4 October 1995	12.10.95

Name and mailing address of the ISA	Authorized officer
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